SURGERY

VOL. 9 APRIL, 1941 NO. 4

Original Communications

COMPARATIVE RESULTS IN THE USE OF LIVING AND PRESERVED FASCIA AS SUTURE MATERIAL IN BONE

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LIVING fascia grafts have been much used in recent years as suture material in the repair of fractures and dislocations. Interesting papers on this subject have been written by Gallie and LeMesurier,[1] Patterson,[2] and Allen.[3] So far as we know, preserved fascia strips have been little used as suture material in fractures, and the only report of such use that we have at hand is that of Patterson,[2] who in one case used preserved human fascia lata to suture a fractured clavicle through drill holes in the fragments. The fascia strip used in this case had been left over from a hernia operation ten days before and preserved in Scott's acetone-alcohol-aqueous solution of mercurochrome in the meantime. The result obtained was just as good as the results obtained in other cases in which living fascia strips had been used.

Experimental work, showing the fate of living fascia transplanted into bone, has been done by Kernwein, Fahey, and Garrison.[4] They have shown that ossification of such transplants occurs.

The fate of preserved fascia grafts when transplanted into soft parts to repair defects was shown by experiments published by Koontz in 1926[5] and in subsequent years, but we know of no experimental work that has been done showing the fate of preserved fascia when transplanted into bone. We have, therefore, performed twenty-eight experiments on dogs, in which both living and preserved fascia were transplanted into bone in different ways, in order to show the fate of both types of fascia and to note any differences that might occur in the fate of the two types. In a few instances the fascia strips (both types) were

Received for publication, May 13, 1940.

transplanted in such a manner that they had no function to perform, but in most instances they were given the function of holding separated bony fragments together.

Experimental.—The following is a record of some of the experiments. Experiments representing all the types of reactions obtained are given below. It is thought unnecessary to record each experiment in detail as this would entail a great deal of repetition. Dogs were used in all the experiments, and, whenever alcohol-preserved fascia was implanted, it was implanted on the right side of the animal, and likewise, living fascia was always implanted on the left side of the animal. This was done to avoid confusion in interpreting results.

EXPERIMENT K1 (Oct. 17, 1935).—*Fascia in Pubic Bone:* Midline incision over symphysis pubis. The ramus of the pubic bone was exposed on the left side, just lateral to insertion of left rectus muscle. About one-third of the thickness of the bone was chiseled away, exposing the medullary cavity. A strip of rectus sheath was excised and sutured around the bone, the flat side of the strip lying in the chiseled notch. The muscle and subcutaneous tissue were then sutured over the site of the operation. The ramus of the pubic bone on the right side was then exposed, and an alcohol-preserved strip of dog fascia lata was sutured in a similarly chiseled notch on this side. The wound was closed.

On Nov. 30, 1935 (44 days after operation), the dog was killed. The site of the fascial implantation was located on each side by the notch in the bone and by the silk sutures with which the strip was sutured in place. There was no callus formation. Very little fascia was seen in the notch on the left side, but a thin strip was visible on the right side.

EXPERIMENT K2 (Nov. 7, 1935).—*Fascia in Femur:* Left rectus incision. A piece of aponeurosis of the external oblique muscle was removed and split in two strips, one of which was placed in 70 per cent alcohol and the other in salt solution. Incision was then made over the left femur, with a mesial approach. The femur was exposed, and a hole was bored through it. The strip of fascia, which had been placed in salt solution, was then placed through the drill hole and tied around the lateral surface of the femur. The knot was transfixed and sutured with black silk. The wound was closed.

A similar operation was done on the right side, using the strip of fascia that had been dropped into 70 per cent alcohol at the beginning of the operation about three-quarters of an hour before.

On Nov. 29, 1935 (22 days after operation), the dog died. Autopsy showed a little evidence of the fascia remaining on each side. The holes in the bones were located on both sides, and the silk sutures showed the sites of implantation. There was no callus formation.

EXPERIMENT K3 (Nov. 14, 1935).—*Fascia in Scapula:* Midline abdominal incision, and a large piece of rectus sheath removed. Half of fascia was placed in salt solution and half in 70 per cent alcohol. The wound was closed.

The dog was then turned over, and the left scapular region was prepared for operation. Incision was made over left scapula. The muscle was separated, and the posterior end of the scapula was split with a saw in a longitudinal direction for about 1.5 inches. Holes were bored on each side of the slit, and a strip of rectus sheath from that which had been placed in salt solution was threaded through the holes and tied so as to steady the slit. The knot was transfixed with silk. The wound was closed.

On Nov. 21, 1935, the right scapula was operated upon in exactly similar fashion to the operation done on the left scapula on Nov. 14, except that a strip of alcohol-preserved rectus sheath, removed from the dog at the first operation, was used instead of living fascia.

On Jan. 9, 1936 (49 days after the first operation and forty-two days after the second operation), both scapular regions were explored. A firm ridge of healing could be felt in the bone on each side. The fascia on each side was identified by the transfixed silk suture. The fascia had partially disappeared, but more was left on the right side than on the left.

EXPERIMENT K5 (Dec. 14, 1935).—*Rib Fusion Operation:* An incision was made over the right ribs, at about the junction of the upper and middle thirds of the chest. Two ribs were exposed. The periosteum was cleaned off, and the muscles were removed from between them. The cortex was then removed from the adjacent edges of the two ribs, and the ribs were brought together by tying around them, in two places, strips of dog fascia removed a week previously and preserved in 70 per cent alcohol. The more anterior strip was tied around the rib twice. The wound was closed.

On Jan. 25, 1936 (42 days after operation), the site of operation was explored, and the two ribs were found to be firmly fused by bony union.

EXPERIMENT K6 (Dec. 21, 1935).—*Rib Fusion Operation:* Two strips of fascia lata were removed from the left thigh, and the wound was closed. An operation exactly similar to that done in the previous experiment was then performed upon this dog, except that living fascia removed from the thigh was used instead of preserved fascia.

On Jan. 30, 1936 (40 days after operation), the site of the operation was explored, but no bony union was found between the ribs that had been tied together with the fascia strips. It was felt that this was due to the fact that the knots had possibly slipped somewhat and the ribs had not been held in close enough apposition.

EXPERIMENT K11 (Oct. 15, 1936).—*Suture of Olecranon With Living Fascia:* Incision was made over the left elbow. The olecranon was sawed in two. Holes were drilled through both fragments, and the fragments were sutured together with a strip of autogenous fascia lata removed from the left thigh. The wound was closed, and a plaster cast was applied.

On Jan. 27, 1937 (104 days after operation), a specimen was removed. There was evidence of firm union. X-ray showed bony union (Fig. 1). Microscopic section showed the fibers of the implanted fascia to be intact in the drill holes, but there was no ossification of the fascia (Fig. 7), although there was some encroachment on it by new bone at the sides of the drill holes.

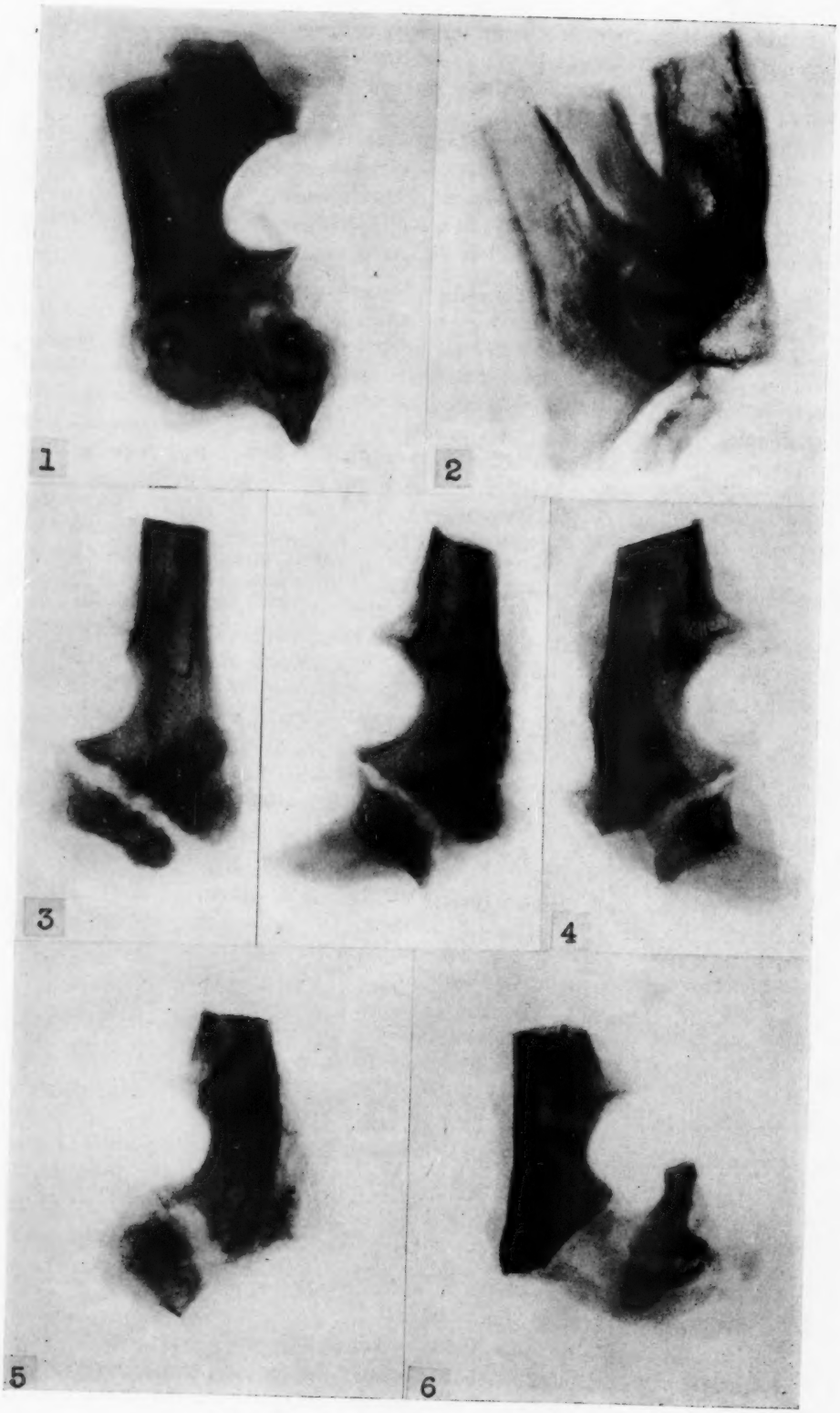
EXPERIMENT K12 (Oct. 31, 1936).—*Suture of Olecranon With Preserved Fascia:* The right olecranon was exposed and sawed in two. It was then sutured with alcohol-preserved ox fascia lata, using the same technique as in the previous experiment. The wound was closed, and the cast was applied.

On Nov. 20, 1936, the cast had come off.

The dog was examined on March 20, 1937. Fragments were nicely approximated, but there was possibly very slight motion.

On May 25, 1937, there was slight motion and obviously only fibrous union.

On May 26, 1937 (7 months after operation), a specimen was removed. X-ray showed no bony union (Fig. 2). Microscopic section showed the fascia fibers to be intact, but there was no ossification of the fascia.



Figs. 1-6.—See opposite page for legend.

EXPERIMENT K13 (Nov. 10, 1936).—*Living Fascia in Olecranon:* Left olecranon was exposed, sawed in two, and sutured as above, using a strip of autogenous fascia lata removed from the left thigh. The wound was closed, and a plaster cast was applied.

On March 20, 1937 (4½ months after operation), a specimen was removed. Union appeared to be firm. X-ray showed fair apposition and some callus, but apparently no bony union from an x-ray standpoint, although clinically there was good bony union (Fig. 3). Microscopic sections showed osteoid tissue between the fragments, and, where the fascia traversed the bone, it had been largely replaced by bone (Fig. 8).

EXPERIMENT K14 (Nov. 12, 1936).—*Preserved Fascia in Olecranon:* The right olecranon was exposed, sawed in two, and then sutured by the technique described above, with a strip of alcohol-preserved fascia lata of dog. The wound was closed, and a cast was applied.

On Dec. 9, 1936 (twenty-seven days after operation), the dog died. Autopsy showed union of the fragments, but there was possibly very slight motion, suggesting that union was not quite complete. X-ray showed partial bony union (Fig. 4). Microscopic sections showed osteoid tissue between the fragments, and the drill holes in the bone contained fascia running into the space between the fragments and containing osteoid cells (Fig. 9).

EXPERIMENT K15 (Dec. 3, 1936).—*Living Fascia in Olecranon:* The left olecranon was exposed, sawed in two, and sutured in the usual manner with a strip of fascia from the left thigh of the same dog. The wound was closed, and a cast was applied.

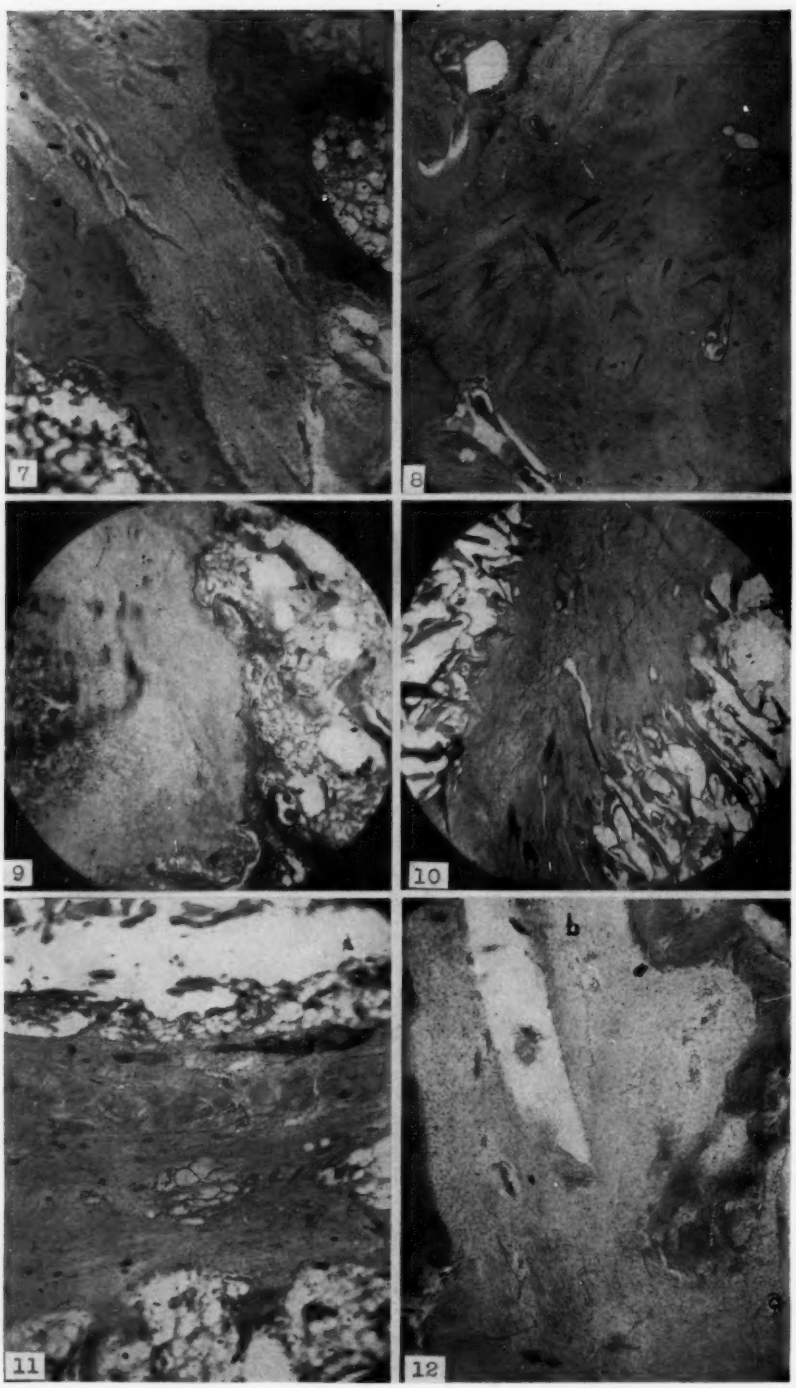
April 17, 1937.—*Preserved Fascia in Olecranon:* The right olecranon was exposed, sawed in two, and sutured in the usual manner with a strip of alcohol-preserved dog fascia lata. The wound was closed, and a cast was applied.

There was apparently firm union on both sides on May 25, 1937.

On June 17, 1937 (6½ months after the first operation and two months after the second operation), the dog was killed, and a specimen was removed from each elbow. Examination showed a wide separation of the fragments on the left side and fibrous union on the right side. X-ray of the specimens showed nonunion on the left side (Fig. 6), and incomplete union with some callus thrown out on the right side (Fig. 5). Microscopic sections of the left elbow showed the fascia intact running through the bone and across the defect between the separated fragments. Sections from the right elbow showed osteoid tissue between the fragments and osteoid cells in the fascia running through the bone.

EXPERIMENT K17 (Dec. 19, 1936).—*Living Fascia in Olecranon:* The left olecranon was exposed, sawed in two, and sutured in the usual manner with a strip of fascia lata removed from the thigh of the same dog. The wound was closed, and a cast was applied.

Figs. 1 to 6.—Fig. 1: K11. Suture of olecranon with living fascia strips. Specimen removed and x-rayed 104 days after operation. Bony union. Fig. 2: K12. Suture of olecranon with preserved fascia. Cast came off in less than three weeks after operation. Specimen removed and x-rayed seven months after operation. No bony union. Fig. 3: K13. Suture of olecranon with living fascia strip. Specimen removed and x-rayed 4½ months after operation. Bony union not complete from an x-ray point of view, although clinically and microscopically (Fig. 8) there was good bony union. Fig. 4: K14. Suture of olecranon with preserved fascia lata. Specimen removed and x-rayed 27 days after operation. Partial bony union. Fig. 5: K15. Suture of right olecranon with preserved fascia lata strip. Specimen removed and x-rayed 3 months after operation. Some callus thrown out. Microscopic section of this specimen showed osteoid tissue between the fragments and osteoid cells in the fascia running through the bone. Fig. 6: K15. Suture of left olecranon with living fascia strip. Specimen removed and x-rayed 6½ months after operation. Nonunion, presumably due to poor immobilization. Microscopic sections of this specimen showed the fascia intact running through the bone and across the defect between the separated fragments.



Figs. 7 to 12.—Fig. 7: K11. Photomicrograph showing living fascia strip in drill hole in bone 104 days after operation. No ossification of fascia. X-ray (Fig. 1) shows bony union. Fig. 8: K13. Photomicrograph of specimen shown by x-ray in Fig. 4. The implanted fascia has largely been replaced by osteoid tissue. Fig. 9: K14. Photomicrograph of specimen shown in Fig. 4, showing osteoid cells in fascia strip. Fig. 10: K17. Photomicrograph of specimen shown in Fig. 13, showing osteoid tissue in fascia. Fig. 11: K18. Photomicrograph of specimen shown in Fig. 14, showing osteoid tissue and fascia. Fig. 12: K25. Microscopic section of specimen shown in Fig. 19. Note osteoid tissue between fragments (*a*) and also the fascia in the drill holes (*b*).

On Jan. 14, 1937 (26 days after operation), the dog died. He was apparently getting good union, but union was not complete. X-ray showed beginning of bony union (Fig. 13). Microscopic sections showed osteoid tissue between the fragments and also in the fascia strips running through the bone (Fig. 10).

EXPERIMENT K18 (Dec. 19, 1936).—*Preserved Fascia in Olecranon:* The right olecranon was exposed, sawed in two, and sutured in the usual manner, using a piece of alcohol-preserved fascia lata removed from the animal in experiment K17. The wound was closed, and a cast was applied.

On Jan. 27, 1937 (39 days after operation), the dog died. A specimen was removed, and x-ray showed no union (Fig. 14). Microscopic sections showed osteoid tissue between the fragments, but more osteoid tissue in the fascia running through the drill holes in the bone. The original fascia could be seen encroached upon on all sides by osteoid tissue (Fig. 11).

EXPERIMENT K19 (Jan. 21, 1937).—*Living Fascia in Olecranon:* The left olecranon was exposed, sawed in two, and sutured in the usual manner with a strip of autogenous fascia lata from the left thigh. The wound was closed, and a cast was applied.

On Jan. 23, 1937, it was discovered that the cast had come off the previous day. Another cast was applied. There was considerable swelling of leg, but wound looked well.

The dog was examined on March 20, 1937. Fragments were nicely approximated, but there was some motion.

April 15, 1937.—*Preserved Fascia in Olecranon:* The right olecranon was exposed, sawed in two, and sutured in the usual manner, with a strip of alcohol-preserved dog fascia lata. The wound was closed, and a cast was applied.

The dog was examined on May 25, 1937. There was firm union on the left side and apparently firm union on the right side.

On June 17, 1937 (5 months after first operation and 2 months after second operation), the dog was killed, and specimens were removed. There was possibly slight motion on the left side, but none on the right. X-ray showed bony union of both sides (Figs. 15 and 16). Microscopic sections of left elbow showed osteoid tissue between the fragments, but the drill holes were not shown in the section. Sections of right elbow showed osteoid tissue present, but it was not clear whether it was in the drill holes, or between the fragments.

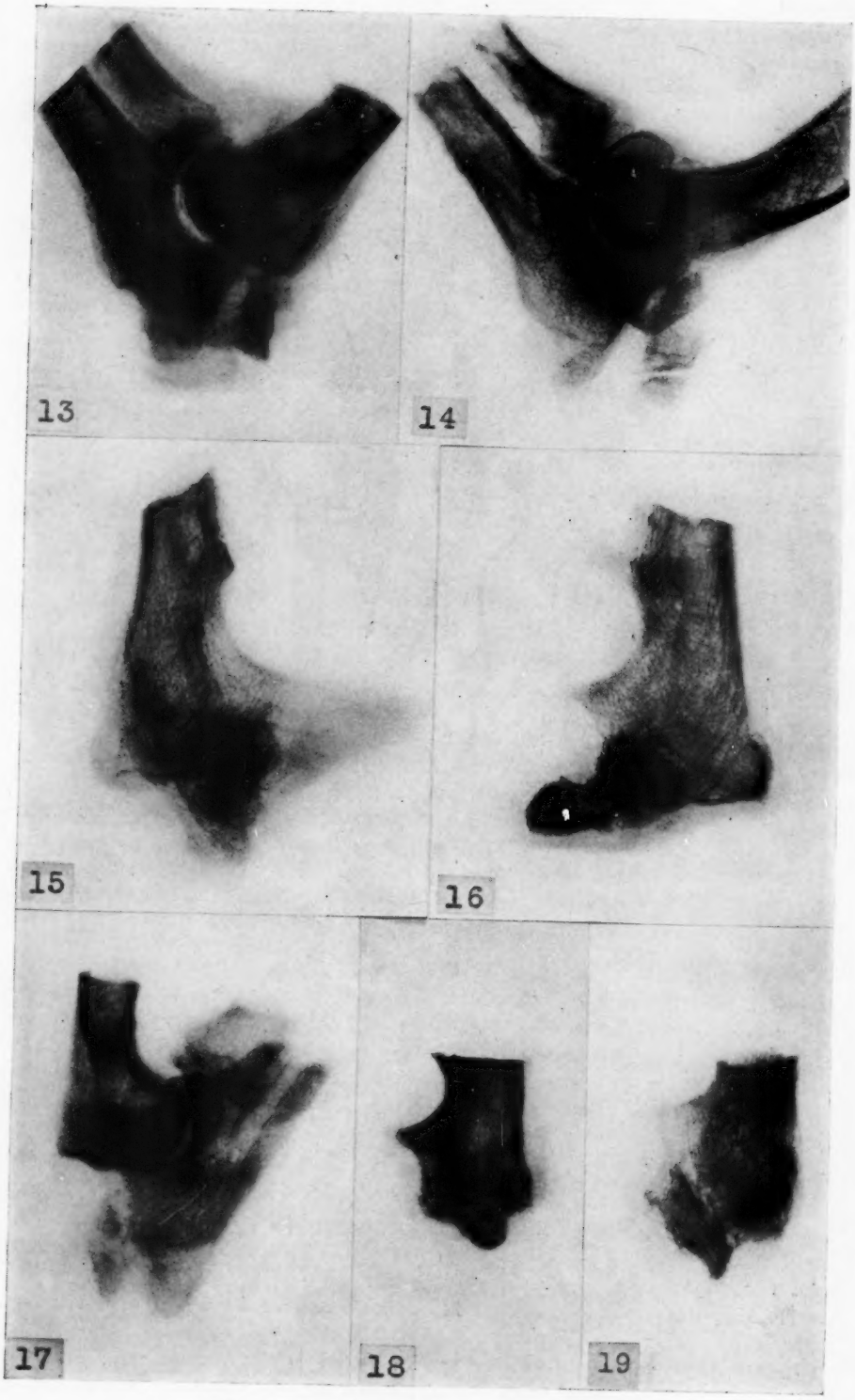
EXPERIMENT K20 (Jan. 23, 1937).—*Preserved Fascia in Olecranon:* The right olecranon was exposed, sawed in two, and sutured in the usual manner with a strip of alcohol-preserved fascia lata removed from animal in Experiment K19 on Jan. 21. The wound was closed, and a cast was applied.

On Feb. 27, 1937 (35 days after operation), the dog died, and a specimen was removed by the laboratory technician. X-ray showed bony union (Fig. 17). Microscopic sections showed osteoid tissue between the fragments. The fascia in the drill holes was still present unchanged and showed no osteoid tissue.

EXPERIMENT K24 (Dec. 23, 1937).—*Ox Fascia in Olecranon:* The right olecranon was exposed, sawed in two, and sutured in the usual manner with a preserved strip of ox fascia lata (commercially prepared).* The wound was closed, and a cast was applied.

The dog was examined on Jan. 27, 1938. Fragments were in apposition, and apparently good union was in progress.

On March 10, 1938 (76 days after operation), a specimen was removed. Firm bony union was found on gross examination. X-ray showed firm bony union, with apparently beginning calcification of the fascia strips going around the olecranon (Fig. 18).



Figs. 13-19.—See opposite page for legend.

EXPERIMENT K25 (March 19, 1938).—*Ox Fascia in Olecranon:* The right olecranon was exposed, sawed in two, and sutured in the usual manner with a strip of preserved ox fascia lata (commercially prepared),* which had been removed from the tube in which it had been put up and soaked in 70 per cent alcohol since Dec. 16. The wound was closed, and a cast was applied.

On May 7, 1938 (49 days after operation), the dog was killed. Gross examination showed good bony union. X-ray also showed bony union (Fig. 19). Microscopic sections showed osteoid tissue between the fragments and also in the fascia in the drill holes (Fig. 12).

DISCUSSION

In these experiments, where conditions were similar, the fate of living fascia strips and preserved fascia strips when implanted in bone was exactly the same. In suture of the olecranon both with living and preserved fascia strips bony union was obtained in all of the cases where immobilization was completed during the healing process. In our first experiments we did not apply casts and found that invariably we got fibrous union with both types of fascia. In the later cases in which we obtained fibrous union, it always occurred in instances in which we were not able to keep the cast on for the proper length of time. (Dogs tend to chew their casts off, and it is often difficult to keep casts on them.)

Both the living and preserved fascia strips used as suture material in bone underwent ossification at variable periods of time, the earliest time observed being twenty-six days. It is probable that the process begins much earlier than this. It seems that the better the fragments are apposed and immobilized, the earlier ossification takes place. In one case in which living fascia had been used as suture, and in which there was poor immobilization with consequent nonunion, the fascia strip was present unchanged in the drill holes five months after operation, and, in a similar case in which preserved fascia had been used, it was present unchanged seven months after operation.

In cases in which fascia was placed in bone, but given little or no function to perform (Experiments K1, K2, and K3), there was no ossification whatsoever, and almost complete absorption of the fascia

*Johnson & Johnson, New Brunswick, N. J.

Figs. 13 to 19.—Fig. 13: K17. Suture of olecranon with living fascia lata strip. Specimen removed and x-rayed 26 days after operation. Apparently getting good union, though not yet complete. Fig. 14: K18. Suture of olecranon with preserved fascia lata strip. Specimen removed and x-rayed 39 days after operation. Apparently no union, although microscopic sections showed osteoid tissue between the fragments and more osteoid tissue in the fascia running through the drill holes in the bone. Fig. 15: K19. Suture of right olecranon with preserved fascia lata strip. Specimen removed and x-rayed 2 months after operation. Bony union. Microscopic sections confirm this. Fig. 16: K19. Suture of left olecranon with living fascia strip. Specimen removed and x-rayed 5 months after operation. Bony union. Microscopic sections confirm the diagnosis. Fig. 17: K20. Suture of olecranon with preserved fascia lata strip. Specimen removed and x-rayed 35 days after operation. Bony union. Microscopic sections confirm this. Fig. 18: K24. Suture of olecranon with ox fascia lata (commercially prepared). Specimen removed and x-rayed 76 days after operation. Bony union. Fig. 19: K25. Suture of olecranon with ox fascia lata (commercially prepared). Specimen removed and x-rayed 19 days after operation. Bony union.

(both living and preserved) in comparatively short periods of time. This is not in accord with the conclusions of Kernwein, Fahey, and Garrison,[4] who state that "lack of function had no demonstrable effect" on the fate of fascia in bone. However, it is in accord with the conclusions of Rehn,[6] and of Lewis and Davis,[7] published in 1910 and 1911 respectively. These authors demonstrated that grafts of tendon and fascia behave quite differently when they are given a function to perform than when they are simply implanted into subcutaneous tissue. When given a function to perform, they do not show any tendency to be absorbed. When implanted in subcutaneous tissue, they rapidly decrease in size, do not readily have the circulation re-established, and become surrounded by phagocytes and round cells. This work was not done with bone, but our experiments would seem to indicate that fascia behaves in the same way in bone, so far as absorption is concerned, as it does elsewhere.

CONCLUSIONS

1. Good results were obtained in suturing fractures of the olecranon in dogs, using both living and alcohol-preserved fascia strips, provided the parts were properly immobilized.

2. No distinction could be made between the results obtained in the two types of fascia used, either functionally, or in so far as shown by gross, microscopic, and x-ray examinations.

3. Ossification of both types of fascia, by replacement of fascia by ingrowing bone, occurred as union of the fragments was accomplished.

4. In cases in which immobilization was incomplete, resulting in fibrous union, both types of fascia were found intact months after implantation.

5. When fascia (both living and preserved) was implanted in bone, with no function to perform, rapid absorption took place.

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STUDIES ON SHOCK*

III. Variability of the Shock Syndrome in Toxic Drug Shock

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WE HAVE been interested in the condition of hemorrhage and shock and its treatment by various infusions.[1, 2] Animal experiments were performed in which profound shock was produced by various means. The main criteria employed in determining and evaluating the severity of shock were low blood pressure, acidosis, as expressed by blood CO_2, and hemoconcentration, as expressed by hemoglobin values. The blood pressure reflects the state of vasomotor tone, the blood CO_2 the state of tissue oxygenation (and indirectly the adequacy of the peripheral circulation), and the hemoglobin values indicate the plasma-cell ratio and changes in the degree of capillary permeability. In non-anesthetized animals the additional clinical symptoms of prostration, labored respiration, defecation, urination, etc., were recorded. We were impressed by the observation that an animal could present the typical clinical picture of shock without the presence of all three criteria stated above; also that no one of these criteria by itself could be expected to indicate the presence or degree of shock. Moon,[3] in his recent monograph, defines shock as "a circulatory deficiency not cardiac nor vasomotor in origin, characterized by a decreased volume of blood, reduced cardiac output (volume flow of blood), and by hemoconcentration" (page 187), and at another point makes the statement that "hemoconcentration is the earliest detectable manifestation of shock as well as the most accurate index of its severity" (page 184). Our experience did not confirm this point. In a number of experiments we observed that no appreciable hemoconcentration occurred despite death of the animal from experimental shock; whereas, in other experiments definite hemoconcentration developed during shock and yet the animal recovered from a state which might be classified as extremely severe when judged by the degree of hemoconcentration.

We employed various drugs in order to produce shock: histamine,[4] peptone,[5] croton oil, and anesthesia.[6] There was no constancy in the effects of the above drugs when used on anesthetized and unanesthetized dogs,[7] nor was there any constant correlation between the dose of the drug and the production of shock in the individual animal in our forty-six experiments.

METHODS

Dogs varying in weight from 10 to 25 kg. were employed. In one group of animals the right carotid artery was cannulated under light ether anesthesia for the purpose of obtaining blood samples and recording blood pressure.[1] Several hours

*Aided by the A. B. Kuppenheimer Fund.
Received for publication, June 5, 1940.

TABLE I

EXPERIMENT NO.	DOG WEIGHT (KG.)	INITIAL VALUES			ANESTHESIA	AGENT USED TO PRODUCE SHOCK‡	FINAL VALUES				HEMOCONCENTRATION		REMARKS
		BLOOD PRESSURE	ARTERIAL CO_2	HEMOGLOBIN SAHLI (%)			INTERVAL SINCE ADMINISTRATION OF AGENT (HR.)	BLOOD PRESSURE	ARTERIAL CO_2	HEMOGLOBIN SAHLI (%)	DEGREE*	% CHANGE	
1	16.3	160/110	39.6	113	None	Histamine† 5.5 mg. i.v.	2	65/55	8.1	152	4+	+36	Died after drawing of last blood sample
2	22.3	160/110	34.8	101	None	Histamine 15 mg. i.v.	3	125/95	14.6	132	4+	+31	Survived; marked acidosis and hemoconcentration
3	18.5	160/100	34.3	108	None	Histamine 22 mg. i.v.	2.5	95/65	20.9	107	0	0	Died 45 min. after drawing last blood sample
4	15.9	140/90	37.5	107	None	Histamine 57 mg. i.v.	2.5	120/90	24.1	116	+	+ 8	Survived; only moderate acidosis; resistant to histamine
5	16.3	180/110	40.3	95	None	Croton oil 0.08 c.c. i.p.	5	145/130	27.9	128	4+	+35	Typical croton oil shock; died next morning
6	13	155/100	34.4	95	None	Croton oil 0.05 c.c. i.p.	5.5	140/100	25.9	120	3+	+26	Hemoconcentration main change; dead next morning

7	19.1	165/110	44.2	101	None	Croton oil 0.15 c.c. i.p.	12	140/105	43.2	128	3+	+27	Hemoconcentration only; survived.
8	10.9	175**	41.6	80	Nembutal	Peptone§ 25 Gm. i.v.	1.25	50**	7.7	101	3+	+26	Typical peptone shock; died 3¾ hr. later
9	13.2	150**	44.3	84	Nembutal	Peptone 40 Gm. i.v.	4.5	120**	16.6	124	4+	+48	Blood pressure fell to 50 and rose to 120 despite marked acidosis and hemoconcentration; killed after 5.5 hr.
10	12.3	155**	42.3	88	Nembutal	Peptone 34 Gm. i.v.	5.5	70**	13.7	92	0	+ 4	Profound acidosis and low blood pressure, yet dog lived 6 hr. in such profound shock without any hemoconcentration
11	10.9	160**	50.4	84	Nembutal	Peptone 38 Gm. i.v.	8	90**	19.5	100	2+	+19	Marked acidosis; no parallel change in blood pressure and hemoconcentration after 8 hr.; dead, 10 hr.
12	15.9	135**	58.1	80	Nembutal	None	6.5	90**	42.3	108	4+	+35	Both dogs survived; hemoconcentration most marked change
13	14.1	160	57.8	92	Nembutal	None	8.25	115	42.9	111	3+	+21	

*Hemoconcentration is graded from 0 to 4+, depending on the percentage increase from the initial value.
†Histamine HCl.
‡*i.v.*, Intravenously; *i.p.*, intraperitoneally.
§Merck.
**Mean pressure.

were allowed to elapse for recovery, so that unanesthetized dogs were used. In another group all experiments were done on dogs anesthetized with sodium pentobarbital or morphine-ether. Histamine and peptone, dissolved in small quantities of saline solution, were injected intravenously. The croton oil was suspended in olive oil and administered intraperitoneally.

RESULTS

Table I summarizes data of representative experiments. The results are arranged according to the agent employed to produce shock. Histamine and croton oil were given to unanesthetized dogs and blood pressure was measured with a tycos anaeroid gauge by means of which systolic and diastolic levels were recorded; other experiments were done under anesthesia and the mean arterial pressure recorded (mercury manometer). Anesthesia per se may cause the development of the shock syndrome,[6] necessitating a series of control experiments with sodium pentobarbital or morphine-ether anesthesia only.

Experiments 1 and 8 represent the typical shock syndrome; following administration of histamine or peptone, blood pressure and arterial CO_2 fell progressively while hemoglobin values rose until death. On the other hand, the animals in Experiments 3 and 10 died in shock and, yet, no hemoconcentration occurred. In Experiments 6 and 7 marked hemoconcentration resulted without particular fall in blood pressure or arterial CO_2. In Experiment 4 blood pressure and hemoglobin were not appreciably altered in the presence of profound shock, wherein acidosis was the outstanding feature. In Experiment 11 marked acidosis occurred early, and only as the experiment progressed did blood pressure fall and a moderate hemoconcentration appear.

DISCUSSION

Histamine and peptone are powerful capillary poisons, paralyzing capillary tone and increasing the area of the vascular bed. Histamine would seem to be the ideal agent for the production of shock. It is a pure substance which can be given in concentrated and accurate amounts. Yet, the results obtained with dogs were extremely variable; one animal would pass into a state of profound shock from a given dose of histamine; another scarcely would be affected. Efforts to produce comparable degrees of shock by repeated doses or constant injection of histamine also failed, for the results were inconstant. In the "histamine experiments" listed in Table I, all dogs were in profound "shock" after the injection of histamine, but the subsequent course and outcome were extremely varied.

Peptone was even more unreliable in its action than histamine. In some animals moderate doses did not cause shock, while large doses often resulted in an irreversible and incurable* degree of shock.

One would expect the injection of such large doses of both histamine and peptone to cause hemoconcentration since they produce dilatation

*Results of fluid therapy in shock will be reported separately.

and increased permeability of the capillaries and consequent loss of plasma from the circulation. However, in these experiments the extent of hemoconcentration varied between 0 and 4+* and bore no constant relationship to the severity of the shock. Death at times occurred without evidence of hemoconcentration at any stage in the development or progress of the shock syndrome. Hemoconcentration was not a reliable or constant feature of shock in our experience.

Doses of croton oil above 0.05 c.c. given intraperitoneally had an intensely irritative effect upon the peritoneum, producing first a copious serous and later an actual hemorrhagic exudate. The effects of this exudation were reflected in the hemoconcentration present in all of these experiments. In all experiments with croton oil the blood pressure began to drop only terminally. A moderate degree of acidosis occurred in experiments 5 and 6; none was noted in Experiment 7.

Nine control experiments were performed in which dogs were anesthetized with sodium pentobarbital or morphine-ether in order to determine the effects of these agents per se on the dogs. Only two of these animals developed shock and died as a result of anesthesia. Hemoconcentration developed in all cases, and, although alkali reserves fell moderately, acidosis appeared only in the two animals which expired.

SUMMARY AND CONCLUSIONS

1. The production of shock by histamine, croton oil, and peptone is extremely variable both in anesthetized and unanesthetized dogs.

2. No correlation seems to exist between the degree of shock and dosage of drug employed in different dogs.

3. Even when profound shock is produced, changes in blood pressure, alkali reserve, and extent of hemoconcentration vary widely from experiment to experiment.

4. Profound or even fatal capillary shock may occur without the development of hemoconcentration at any stage of its course.

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*See Table I.

STAPHYLOCOCCIC SEPTICEMIA

Treatment by Chemotherapy and Serotherapy

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INVASION of the blood stream by the staphylococcus is a very serious, though infrequent, condition. Reported mortality rates vary between 66 per cent[1] and 91.4 per cent,[2] and Reimann,[3] reviewing large groups of cases, strikes an average of 79 per cent. Recent reports[2, 4-10] of the use of newer therapeutic agents seem to give promise of lowering these figures. Five patients with staphylococcus bacteremia have been under the care of one of us (S. L. G.), 1 in 1934, 1 in 1936, and 3 in 1939 (Cases 1, 23, 27, 29, and 30). These have all survived. The other 3 patients with this condition treated at Michael Reese Hospital in 1939 also survived. These encouraging results, as well as the recent promising reports, prompted us to review all the instances of staphylococcus septicemia treated at the hospital during the years 1934 to 1939, inclusive.

This series includes 32 cases* of staphylococcemia, 19 males and 13 females, in which 14 died. The total mortality was 43.95 per cent (Table I). In each the diagnosis was established by recovery of the organism from the circulating blood stream in pure culture at least once. Twenty-six were *Staphylococcus aureus,* and 6 were *Staphylococcus albus.* In 23 patients it was recorded that the organism was also recovered from the primary or metastatic focus or both.

The condition is not very common. This is borne out by the incidence of only 32 known and proved cases from a total of 98,825 admissions to the hospital over a six-year period. There can be little doubt, however, that the occurrence of staphylococcus bacteremia is much more frequent than is commonly believed. The great majority of osteomyelitis probably follows bacteremia, and it is not unlikely that some patients with multiple furunculosis also have bacteremia, very transient though it may be. Staphylococcus septicemia is encountered less frequently than the streptococcic variety. Stevens[11] gives the ratio of 2:3; Rosenow and Brown,[1] as 1:2; Mendell,[12] as 1:2.3. The mortality, however, has usually been reported higher than that from streptococcus septicemia, and in our

Received for publication, June 5, 1940.

*We are indebted to the following for permission to include the records of their private patients in this report: Case 4, Dr. M. L. Parker; Case 5, Dr. Solomon Strouse; Case 9, Dr. J. Meyer and Dr. M. L. Parker; Case 10, Dr. J. S. Golden; Case 11, Dr. M. L. Leventhal; Case 14, Dr. R. Green; Case 16, Dr. P. Lewin and Dr. S. Sideman; Case 17, Dr. D. H. Levinthal; Case 18, Dr. Mary Shutan; Case 20, Dr. H. Nedoss; Case 23, Dr. Mary Shutan; Case 25, Dr. D. H. Levinthal; Case 26, Dr. C. Cohen; Case 29, Dr. D. H. Levinthal; Case 31, Dr. S. Salinger and Dr. L. Bloch; Case 32, Dr. I. Frank.

experience the duration and the pyemic complications have made the staphylococcic type the one to be dreaded.

One must assume that the natural defense against such a prevalent organism must be very efficient in order to prevent more frequent invasion of the blood stream. The skin and upper respiratory tract are constantly exposed and are subject to frequent subminimal infections through minute abrasions. It has been demonstrated that painting the pharynx with staphylococci or their toxins promotes the formation of antitoxic substances in the body.[13] These are probably the usual means by which a certain antitoxic titer is maintained in the human being. Reichel[14] has shown in experimental animals that, after intravenous injections of *Staphylococcus aureus,* the body defense mechanism can rapidly sterilize the blood stream.

According to Stookey and Scarpellino,[2] the exotoxin elaborated by the staphylococcus can be broken up into several factors, leucocidin, hemolysin, coagulase, a dermonecrotic element, and a lethal toxin. The injection of small amounts (0.5 to 1 c.c. per kilogram of body weight) of this toxin is sufficient to kill experimental animals. These factors of the exotoxin probably account for the sequence of events in invasion of the blood stream through the medium of mycotic emboli arising from the primary focus, and possibly reinvasion from the metastatic foci elsewhere in the body. The amount of toxin in the circulating blood stream cannot as yet be measured. Parish and his associates[15] described a method of titration of the antitoxic content of the blood and showed experimentally that with the antitoxic level elevated the animals survived injections of lethal doses of toxin. Robertson[16] and Weaver[17] have found titration of the antitoxic level in the blood to be of value clinically, especially in prognosis.

In our series the organism entered the body through various portals, of which the skin was the most frequent. The initial skin lesion may be small enough to evade the most careful search. In 9 of our 32 cases the first focus is recorded as osteomyelitis; these may have been of such an origin. In 14 others the skin focus was known, 11 carbuncles or furuncles, 1 infected bulla, 1 laceration, and 1 infection secondary to tricophytosis of the feet. Upper respiratory tract infection preceded the bacteremia in 6 cases, and in 1 case each the origin was puerperal sepsis, urinary tract infection, and a postoperative infection of a nasoplasty incision.

There was considerable variation in the period of time between the appearance of the initial focus of infection and the manifestations of blood stream invasion. In 4 patients there were early symptoms so alarming as to prompt taking blood for culture within forty-eight hours of the known onset of the initial lesion, and in the rest this period varied

TABLE I

ALL PATIENTS IN THE SERIES GROUPED ACCORDING TO THERAPY USED

NO.	DATE	AGE	SEX	SITE OF ORIGINAL LESION	BACTERIAL CULTURES		ASSOCIATED OSTEOMYELITIS	CLINICAL COURSE	RESULT	PER CENT MORTALITY
					LESION	BLOOD				
				Patients Given Supportive Therapy						
1	March, 1934	45	M	Tricophytosis feet	?	Aureus		Protracted	Recovered	
2	August, 1934	15	M	Osteomyelitis	Albus	Albus	+	Protracted	Died	
3	August, 1934	2	F	Osteomyelitis	Aureus	Aureus	+	Moderately severe	Recovered	
4	October, 1934	13	M	Osteomyelitis	Albus	Albus	+	Moderately severe	Recovered	
5	March, 1935	24	M	Upper respiratory		Aureus	+	Moderately severe	Recovered	37.5
6	November, 1935	68	F	Perineal abscess	?	Albus		Protracted	Died	
7	December, 1937	48	F	Carbuncle on forehead	Aureus	Aureus		Protracted	Died	
8	January, 1938	3 wk.	M	Osteomyelitis	Aureus	Aureus	+	Benign	Recovered	
				Patients Treated With Sulfanilamide						
9	July, 1937	61	M	Carbuncle	Aureus	Aureus		Fulminating	Died	
10	August, 1937	22	M	Upper respiratory		Albus		Fulminating	Died	
11	November, 1937	30	F	Puerperal	?	Aureus		Fulminating	Died	100.0
12	May, 1938	10 mo.	M	Osteomyelitis	Aureus	Aureus	+	Fulminating	Died	
13	May, 1938	1 mo.	M	Furuncle	Albus	Albus		Protracted	Died	
14	July, 1938	66	M	Urinary tract	Aureus	Aureus		Fulminating	Died	

				Patients Treated With Sulfanilamide and Antitoxin						
15	July, 1937	6	F	Carbuncle on scalp	Aureus	Aureus	+	Moderately severe	Recovered	
16	February, 1938	20	F	Carbuncle on neck	Aureus	Aureus		Protracted	Died	
17	April, 1938	8	M	Furuncle	Aureus	Aureus	+	Moderately severe	Recovered	
18	February, 1938	12	F	Upper respiratory		Aureus	+	Moderately severe	Recovered	33.0
19	December, 1938	14	F	Bulla toe	Aureus	Aureus	+	Fulminating	Died	
20	September, 1938	50	F	Traumatic laceration	?	Aureus		Benign	Recovered	
				Patients Treated With Antitoxin						
21	April, 1936	14	M	Upper respiratory	Aureus	Aureus		Fulminating	Died	
22	July, 1936	27	M	Furuncle on forehead	?	Aureus		Fulminating	Died	
23	December, 1936	8	F	Upper respiratory	Aureus	Aureus	+	Protracted	Recovered	50.0
24	November, 1937	12	M	Upper respiratory	Aureus	Aureus	+	Moderately severe	Recovered	
25	July, 1938	10	M	Osteomyelitis	Aureus	Aureus	+	Moderately severe	Recovered	
26	September, 1938	4	F	Osteomyelitis	Aureus	Aureus	+	Protracted	Died	
				Patients Treated With Sulfapyridine						
27	February, 1939	2	F	Osteomyelitis	Aureus	Aureus	+	Benign	Recovered	
28	May, 1939	11	M	Osteomyelitis	Aureus	Aureus	+	Moderately severe	Recovered	0
29	December, 1939	12	F	Osteomyelitis	Aureus	Aureus	+	Moderately severe	Recovered	
				Patients Treated With Sulfapyridine and Antitoxin						
30	February, 1939	10	M	Carbuncle on neck	Aureus	Aureus		Fulminating	Recovered	
31	April, 1939	24	F	Nasoplasty	?	Albus		Fulminating	Recovered	0
32	June, 1939	2	M	Furuncle on nose	Aureus	Aureus		Fulminating	Recovered	

up to a maximum of several weeks. There are several factors which may account for this. Different strains of organisms vary in their virulence. The organism may be introduced directly into the blood stream, as by a puncture wound, or into tissues which may react rapidly to prevent spread. Whether some strains of bacteria produce a toxin rich in coagulase so that there is thrombosis and early release of mycotic emboli is a matter of speculation.

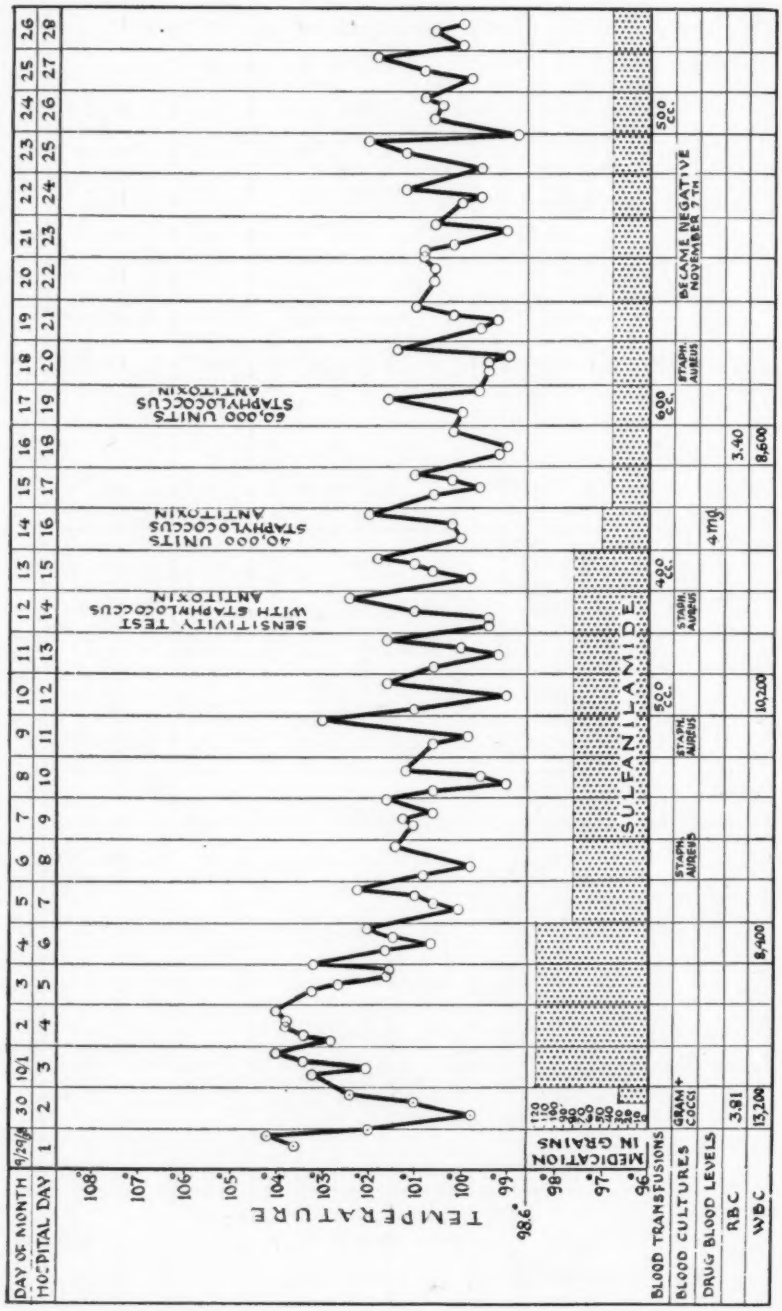

Fig. 1.—Temperature, laboratory data, and treatment in Case 20.

CLINICAL PICTURES AND CASE REPORTS

The clinical pictures merit some detailed description, though in many respects they followed the patterns previously described by many authors. All patients have had temperatures; the ones who died invariably had temperatures above 104°. Toxemia was evident in all, marked in many. Chills were common and severe.

Three patients had a surprisingly benign clinical course, with symptoms that were not pronounced, and relatively low temperatures. An example of this is Case 20 (Fig. 1).

CASE 20.—A 50-year-old female was admitted to the hospital on Sept. 29, 1938. She had sustained a laceration of her right leg three weeks previously, and it had healed rapidly and uneventfully. On the day before admission her temperature rose to 102°* and she complained of pain in the right iliac region and in her left hip. There were no abnormal physical findings except tenderness in these areas. The pain and fever persisted, and on Sept. 30, because of the history, symptoms, and indeterminate fever, blood was drawn for culture. Hemolytic *Staphylococcus aureus* was recovered in pure culture. Sulfanilamide was given, 120 gr. in twenty-four hours for four days, and the dose was then reduced to 80 gr. in twenty-four hours. There was little change in the clinical picture. On Oct. 14 the blood sulfanilamide level was 4 mg. per 100 c.c. On Oct. 6 and 9 *Staphylococcus aureus* was again grown in pure culture from the blood. On Oct. 12, 40,000 units of staphylococcus antitoxin were given intramuscularly. Transient urticaria followed. On Oct. 17, 60,000 units of staphylococcus antitoxin and 600 c.c. of blood were given intravenously. This was followed by some improvement in the general condition and a reduction in temperature to about 101°. On Oct. 17 and 27 staphylococci were again reported grown in pure culture from the blood. During this period there was slow but gradual improvement, and on Nov. 7 culture of the blood proved sterile. The temperature dropped to normal by lysis, and on Nov. 12 the patient was well enough to be sent home.

The clinical course in ten patients was moderately severe, with temperatures of at least 102 to 103°, toxemia, and mild anemia. These require no detailed reports. The course in the 19 severely ill patients was fulminating in 11 and protracted in 8. Two examples of fulminating infections merit report in some detail.

CASE 31.—(Fig. 2.) A 24-year-old female had a nasal plastic repair on April 18, 1939. Forty-eight hours later her temperature rose to 101.2° R., and she had severe pain at the site of operation. There was some diffuse swelling and redness of the nose. Sulfanilamide was given in 15 gr. (1 Gm.) doses four times daily. The temperature rose gradually, reaching 103.4° on April 26. At this time *Staphylococcus albus* in pure culture was reported grown from blood taken for culture on April 24. On April 26 she had a chill; her temperature rose to 105° and she was much more toxic. The dosage of sulfanilamide was increased to 120 gr. (6 Gm.) daily, but the toxicity and temperature persisted, temperature readings reaching 105° on April 28 and 29. Blood sulfanilamide levels were 4 mg. per 100 c.c. on April 27, and 6.6 mg. per 100 c.c. on April 28. On April 29 a repeat culture of the blood

*All temperatures are in degrees Fahrenheit and were taken by rectum.

again revealed *Staphylococcus albus.* At this time the administration of sulfanilamide was stopped, and sulfapyridine was given in doses of 30 gr. (2 Gm.) every four hours. On April 30, 100,000 units of staphylococcus antitoxin were given intravenously. That night her temperature rose to 106° and then dropped to normal, where it remained. On May 1 blood sulfapyridine was 6.2 mg. per 100 c.c. After one week of normal temperature, the patient left the hospital on May 7, fully recovered. At no time was there more than a slight serous discharge from the wound.

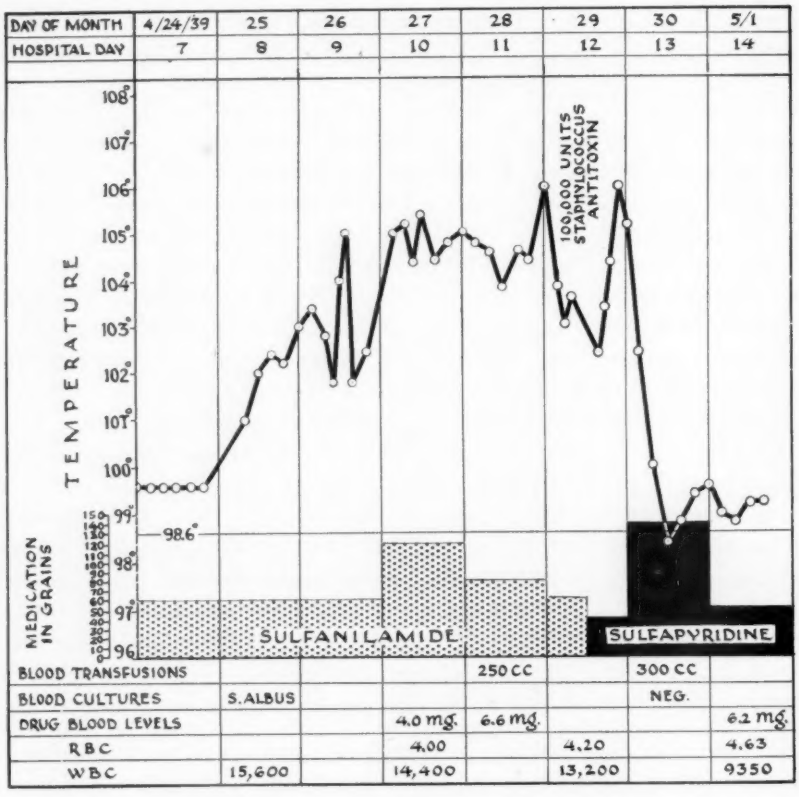
DAY OF MONTH 4/24/39 25 26 27 28 29 30 5/1
HOSPITAL DAY 7 8 9 10 11 12 13 14
TEMPERATURE
108° 107° 106° 105° 104° 103° 102° 101° 100° 99° 98.6° 98° 97° 96°
100,000 UNITS STAPHYLOCOCCUS ANTITOXIN
MEDICATION IN GRAINS
SULFANILAMIDE
SULFAPYRIDINE
BLOOD TRANSFUSIONS 250 CC 300 CC
BLOOD CULTURES S.ALBUS NEG.
DRUG BLOOD LEVELS 4.0 mg. 6.6 mg. 6.2 mg.
RBC 4,00 4,20 4,63
WBC 15,600 14,400 13,200 9350

Fig. 2.—Temperature, laboratory data, and treatment in Case 31.

CASE 30.—(Fig. 3.) A 10-year-old male had a small carbuncle on his neck for one week prior to his admission to the hospital on Feb. 12, 1939. His temperature was 102.8° F., and the family was told that the fever seemed out of proportion to the size and appearance of the lesion. That afternoon, under ethylene anesthesia, crucial incisions were made and frank pus was evacuated. Culture of this pus revealed *Staphylococcus aureus.* In the next twelve hours the patient had three chills, and the temperature rose to 104°. The boy vomited several times and was very toxic, becoming irrational at intervals. His leucocyte count was only 6,900. We felt that we were dealing with a fulminating septicemia, probably staphylococcic, and blood was drawn for culture. Vigorous treatment was instituted without delay. He was given 30 gr. (2 Gm.) of sulfapyridine by rectum every four hours. He received 250 c.c. of blood by indirect transfusion, following which a total of 110,000 units of staphylococcus antitoxin was administered intravenously, diluted in saline solution, in the succeeding eight hours. Fifteen minims of adrenalin solution (1:1,000) was given with this because of the patient's known allergy. His temperature reached 106.6° that night, then dropped rapidly to normal, and remained there except for a

slight transient rise two days later. At this time *Staphylococcus aureus* in pure culture was reported grown from the blood. Vomiting stopped promptly, permitting oral administration of 60 gr. (4 Gm.) of sulfapyridine in divided doses daily for the next two days. It was then stopped because of the rapidly improving general condition, the blood sulfapyridine level being 5.1 mg. per 100 c.c. on Feb. 15. There was a rather unpleasant urticaria from the seventh to the tenth day and a daughter furuncle in the neck which was drained, but otherwise the patient's convalescence was uneventful.

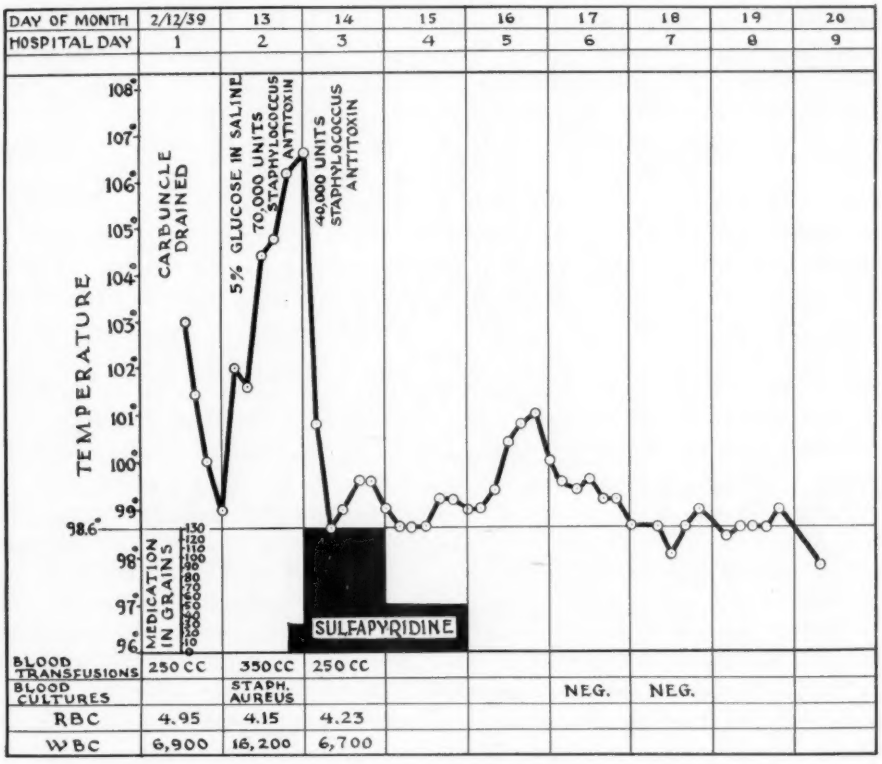

Fig. 3.—Temperature, laboratory data, and treatment in Case 30.

An example of a patient with a severe, protracted clinical course follows:

Case 23.—An 8-year-old female entered Michael Reese Hospital on Dec. 19, 1936. There was a history of a cold, fever, sore throat, and cervical adenitis for two weeks. On admission she was acutely ill. Her temperature was 102° F.; pulse, 116; and respiration, 28. Her throat was edematous and injected, and there were numerous enlarged, tender, cervical lymph nodes. Examination of the ears, chest, abdomen, and extremities revealed nothing abnormal. Red blood count was 4,000,000; hemoglobin, 80 per cent; and leucocyte count, 30,000. The urine was scant in amount, smoky, and contained albumin. Microscopic examination of the sediment showed eight to ten erythrocytes and two to four leucocytes per high-power field.

During the next few days there was little change in the patient's general condition. The urine became more smoky and then definitely bloody. On Dec. 23 the edematous, bulging parapharyngeal space on the right side was incised, but no

pus was obtained. The temperature ranged between 101 and 104°. On Dec. 24 the patient complained of pain which persisted in the right chest and flank. On Dec. 28 there was induration over the fifth rib in the right anterior axillary line. On Dec. 30 this became fluctuant and was incised. Frank pus was obtained from beneath the periosteum of this rib. *Staphylococcus aureus* was grown in pure culture from the blood drawn on Dec. 28, as well as from the pus from the subperiosteal abscess of the rib.

On Jan. 2, 1937, aspiration of the patient's right pleural cavity confirmed the presence of an empyema, and closed drainage was instituted. *Staphylococcus aureus* was grown from another specimen of blood on Jan. 2. The patient's condition became progressively worse. Perinephritic or liver abscess was suspected because of upper abdominal tenderness and distention and continued hematuria and albuminuria. There was some edema, particularly of the extremities. The temperature was septic in character, ranging from 99 to 105°, and the prognosis seemed almost hopeless. On Jan. 15, 10,000 units of staphylococcus antitoxin were given intravenously. This was followed by an anaphylactic reaction of such severity that no further antitoxin therapy was attempted. By Jan. 17, about six weeks after onset of the illness, a large fluctuant mass localized in the lower abdominal wall. This was incised, and about 300 c.c. of pus was evacuated. There was little change in the desperate general condition for the next several weeks. The patient was given a total of twenty-one small blood transfusions, one every few days, during this critical phase of her illness. On Feb. 16 and 17 examination of the ocular fundi established that the right jugular vein was thrombosed. On Feb. 18 surgical exploration of the vein confirmed the thrombosis; it was ligated, and a section was excised for histologic examination. At the same time the right perinephritic and subphrenic spaces were explored, and multiple miliary abscesses of the liver and right kidney were found. During the next several weeks there was a slight but gradual general improvement. The pulse rate dropped from about 160 to about 140, and the temperature averaged between 102 and 103° instead of between 103 and 104°. The empyema cavity was smaller, but the rib drained profusely and sequestration was evident in the roentgenograms. Hematuria and albuminuria decreased gradually. Blood cultures were repeatedly positive, with the exception of one sterile specimen drawn on Feb. 19. On Feb. 27 blood drawn for culture was sterile, and the blood remained so on several subsequent examinations.

On March 6 the entire necrotic fifth rib was removed, and the small residual empyema cavity was unroofed. After several stormy days definite improvement became noticeable and continued slowly, until on May 4 the child was sent home, although a low-grade temperature and a pulse of about 120 persisted.

In April, 1938, the child was readmitted to the hospital with severe back pain and fever. After two weeks an abscess localized and was drained. *Staphylococcus aureus* was grown in pure culture from the pus. Repeated cultures of the blood were negative. After a protracted course of three months the patient left the hospital. At the present time it seems that the child has made a complete recovery.

MORTALITY

The lower mortality rate (25 per cent) in the children under 10 years of age as compared with the adults in our series (Table II) parallels the experiences of other authors, as does the lower death rate (23.5 per cent) in that group of patients with associated osteomyelitis[2, 4, 5, 12, 16, 17] (Table III).

TABLE II

DISTRIBUTION AND MORTALITY IN VARIOUS AGE GROUPS

AGE	NO. OF CASES	DIED	RECOVERED	PER CENT MORTALITY
Under 1 yr.	3	2	1	66.6
1-10 yr.	9	1	8	11.1
10-20 yr.	8	3	5	37.5
20-30 yr.	5	3	2	60.0
30-40 yr.	1	1	0	100.0
40-50 yr.	2	1	1	50.0
50-60 yr.	1	0	1	0.0
60-70 yr.	3	3	0	100.0
Totals	32	14	18	44.0

There were no deaths in the patients whose clinical courses were relatively benign or moderately severe. On the other hand there were 8 deaths in 11 patients whose clinical courses were severe and fulminating. It is significant that the 3 recoveries in this group (Cases 30, 31, and 32) were the patients who received early and adequate treatment with both sulfapyridine and staphylococcus antitoxin. In the 8 patients whose clinical courses were severe and protracted there were 6 deaths. The 2 patients who recovered received only supportive therapy and are striking illustrations of the fact that even before the advent of specific therapy there were occasional recoveries from this condition. Of the 14 deaths, 9 occurred within two weeks, 3 within two to six weeks, 1 after nine weeks, and in 1 the history of onset was unobtainable.

TABLE III

MORTALITY IN CASES WITH AND WITHOUT OSTEOMYELITIS

	TOTAL	RECOVERED	DIED	PER CENT MORTALITY
Osteomyelitis	17	13	4	23.5
Nonosteomyelitis	15	5	10	66.6

Associated diseases, of course, exert an unfavorable influence on recovery. In our series the following complicating conditions were encountered: syphilis in 2 instances, diabetes mellitus in 3, renal infection and urosepsis in 1, and marked arteriosclerosis and coronary sclerosis in 1. In the group of patients with these diseases the mortality, as might be expected, was high (80 per cent).

TREATMENT

Observation and study of the clinical course of the patients in our series lead us to believe that, although staphylococcus septicemia is a serious illness, there are some patients who recover without specific therapy and other patients who will die in spite of any therapy known at the present time. The majority of cases probably fall in a group that

are amenable to newer methods of specific therapy and may not have been benefited by older methods of nonspecific supportive treatment.

It has been very interesting to follow the trend in the treatment of staphylococcus bacteremia during the past few years. Until several years ago treatment was mainly supportive. In our series 8 patients received only supportive therapy. The mortality rate was 37.5 per cent (Table I) in this group. This figure cannot be compared with those in other reports because of the small number of cases in our study. Supportive treatment consisted of rest, sedatives, adequate fluids given orally, parenterally, or both, blood transfusions to transfer antibodies as well as to combat anemia, and attempts at chemotherapy with various dye antiseptics. Treatment of local lesions by rest, heat, and incision and drainage of collections of pus, of course, was carried out. Associated disease processes were treated; e.g., diabetes mellitus, syphilis, renal disease, etc.

In our series various other types of treatment were used, some specific, some nonspecific. These included, among others, tin preparations, staphylococcus toxoid, bacteriophage, and transfusions of blood from immune donors. There have been several case reports claiming beneficial effects following the use of toxoid and bacteriophage. It is impossible to draw any conclusions regarding their efficacy because of their limited use. Theoretically, blood transfusions from immune donors, if available, might be beneficial in the severely ill patients. In contrast to our experiences and results with the use of immune human serum or blood in streptococcic septicemia,[18] we observed no striking or encouraging results following our limited use of immune human blood in staphylococcic septicemia. Furthermore, the difficulty of obtaining such blood in sufficient quantities is great enough to render such therapy impractical, especially inasmuch as specific immune bodies are readily obtainable in the form of commercial antitoxin.

With the advent of sulfanilamide, this drug was employed in the treatment of staphylococcus septicemia with the hope that it would be of as much value as it is in the streptococcus infections. Sulfanilamide alone was used in treating 6 patients. All of these cases terminated fatally. Six other patients were treated with sulfanilamide in combination with staphylococcus antitoxin, and, of these, 4 recovered (Table I). It did not appear to us that sulfanilamide had any specific value in the treatment of staphylococcus septicemia. Several isolated instances of recovery following its use have been reported. Most of these patients had clinical courses that were either moderately severe or protracted, in which groups there is a higher incidence of recovery without the use of specific therapy, as noted previously. Case 20 is an example of this. We do not believe that in this instance we can attribute any specific value to the drug.

Fifteen patients, of whom 11 were 14 years of age or less and 4 more than 14 years old, were treated with staphylococcus antitoxin, either alone, or in combination with sulfanilamide or sulfapyridine (Table IV). Formerly, severe serum reactions following administration of

TABLE IV

MORTALITY IN CASES TREATED WITH STAPHYLOCOCCUS ANTITOXIN*

	NO. OF CASES	OSTEOMYELITIS	NONOSTEOMYELITIS	MORTALITY		TOTAL MORTALITY
				OSTEOMYELITIS	NONOSTEOMYELITIS	
Antitoxin alone	6	4	2	1	2	50.0%
Antitoxin with sulfanilamide	6	4	2	1	1	33.3%
Antitoxin with sulfapyridine	3	0	3			0 %
Totals	15	8	7	2	3	33.3%

*See text for age distribution.

antitoxin deterred us and other physicians from its use. Recent refinements by purification and concentration have reduced the incidence and severity of these reactions. Other authors believe that the use of antitoxin has reduced mortality to about 50 per cent.[2, 4, 5, 19, 20] In our series of 15 cases there was a total mortality rate of 33.3 per cent. In the younger group there were 3 deaths, a mortality of 27.33 per cent; and of the 4 adults 2 died, a mortality of 50 per cent. Our experience, particularly in the more recent cases, where larger doses of antitoxin were employed (100,000 to 180,000 units), leads us to believe that antitoxin is of definite value and that it should be administered early in sufficient dosage. Possibly the use of larger dosages and further improvement in the preparation will increase its effectiveness. The initial dose in adults with severe infections should be at least 100,000 units, following sensitization tests and desensitization where necessary. We used the intravenous route and found that, if the antitoxin is diluted in saline solution, the reactions are not so frequent or severe. It should be given slowly over a period of several hours. In patients with allergic backgrounds or histories of allergic manifestations, adrenalin solution in small doses should be given at the same time. Further administration of antitoxin depends upon the clinical picture. Daily doses should be given, usually in decreasing amounts, until the subsidence of manifestations of the acute phase of the infection.

Sulfapyridine was used in the treatment of all 6 patients with staphylococcus septicemia admitted to the hospital during 1939. In 3 of the patients sulfapyridine was combined with staphylococcus antitoxin. We have reported 2 of these cases,[7] in which a deliberate therapeutic trial of sulfapyridine was made. No other specific therapy was used and both patients recovered. Complete recovery in this group of six consecutive cases (Table I) is very significant.

The initial dose of the drug used was approximately 1.5 grains per pound body weight each twenty-four hours. This dose was continued, maintaining a sulfapyridine level in the circulating blood stream of at least 6.0 mg. per cent, preferably between 6.0 mg. and 9.0 mg. per cent. The drug can be given rectally, and a soluble form is now available for subcutaneous and intravenous use.[21] We have administered it by rectum on several occasions and have found it effective. With subsidence of symptoms, the dose should be gradually reduced.

Mild toxic effects of the drug such as nausea and vomiting are encountered frequently, apparently without relation to the dosage or to the drug blood level. They are probably of central nervous system as well as of gastrointestinal origin.[22] Cyanosis is frequent, especially with high blood levels. Skin rashes and tingling of extremities are also occasionally seen. The more serious manifestations are fortunately less common and are thoroughly discussed in other publications.[22, 23] We have not encountered them in our experience and would not let them deter us from the use of this drug in a disease as severe and fatal as staphylococcus septicemia.

Although our experience with sulfapyridine therapy of staphylococcus septicemia is not extensive, we feel that we can strongly recommend its use. In the 2 cases referred to previously,[7] the control was as adequate as can be exercised in clinical procedure and treatment was followed by rapid sterilization of the blood stream. In all 6 patients, and especially in the 3 patients for whom the use of sulfapyridine was combined with staphylococcus antitoxin therapy, the clinical improvement was very definite and rapid and occurred soon after the institution of treatment.

Undoubtedly further developments in chemotherapy will ensue. Herrell and Brown[10] reported the recovery of a patient following the use of sulfamethylthiazol in a case of staphylococcus sepsis. Fitch[8] reports the recovery of a 10-year-old girl who had a severe, protracted clinical course. Helmholz[24] reported that the drug is bactericidal in vitro to the organisms found in urinary tract infections. These authors and Long[25] think it is at least as efficient as sulfapyridine, and probably less toxic, although it is too early to make accurate comparisons. The future may give us drugs with even more specific action against the staphylococcus.

The mode of action of the chemotherapeutic agents and of staphylococcus antitoxin differ. The exotoxin elaborated by the staphylococci are apparently neutralized by antitoxins, while the bacteria themselves are affected by the drugs in a way as yet not fully understood. Multiplication of the organisms is diminished, and they are in some way sufficiently attenuated to allow their destruction by body defenses. It seems, on theoretical grounds, that synergistic action between the two agents might obtain. A definite and parallel synergistic action between sulfapyridine and antipneumococcic serum against the pneumococcus

has been reported.[22, 26, 27] This hypothesis of synergistic action seems to be confirmed by some interesting work reported by De and Basu.[28] They did experimental work on mice employing sulfanilamide, staphylococcus antitoxic serum, and combination of the two agents in protection against staphylococcal infection. A group of mice inoculated with a certain dose of *Staphylococcus aureus* and untreated all died. Another group, likewise infected with the organism, were treated with sulfanilamide, and 33 per cent survived. Twenty-five per cent of another similar group treated with antitoxin survived. There was 100 per cent survival in a fourth group treated with the same doses of both therapeutic agents. All this evidence is strongly suggestive that combined therapy is more effective than either type of therapy used alone. Meyer[29] reports three cases that recovered following treatment with staphylococcus antitoxin and sulfanilamide and believes there is synergistic action between these agents.

Sound surgical treatment of local lesions is paramount. There is general agreement that, if the infection is in soft tissues, it should be treated conservatively and not manipulated until pus is formed. Heat and possibly x-ray therapy are of value in localizing the infection. When there is a collection of pus, it should be evacuated.

There is at present a distinct trend toward a change in the treatment of osteomyelitis. Until several years ago the teaching was general that acute osteomyelitis was a surgical emergency. In order to avoid stripping of periosteum and further bone destruction, drainage was advocated as soon as even a presumptive diagnosis was made. In several recent reports[30-33] delayed operation and more energetic treatment of the general condition of the patient was carried out. The results reported are good. The use of sulfapyridine and staphylococcus antitoxin should further these ideas. Three cases that seem significant[34] have come to our attention very recently. In each there was a very typical clinical picture of acute osteomyelitis, which subsided completely after conservative management by rest, local heat, and sulfapyridine therapy. There were only minimal x-ray findings of bone destruction several weeks later. Up to the present time (between six weeks and three months after onset), these patients are clinically recovered and have not required surgery.

Early diagnosis of staphylococcus septicemia and institution of treatment even before the diagnosis is established by laboratory procedures are important factors in the reduction of mortality. Any rise in temperature or increase in toxicity above what may be expected from any infected focus, particularly when accompanied by chill, should be sufficient grounds for instituting vigorous treatment. The situation can be compared to the treatment of diphtheria and of meningococcus meningitis. In diphtheria vigorous specific treatment is begun when a suspicious membrane is present in the throat, and no time is lost waiting

for positive culture reports. We urge the institution of vigorous specific therapy, without waiting for blood culture reports, as soon as a patient with a known staphylococcus infection, or a recent history of one, develops graver symptoms than can be accounted for by the local lesion. For example, in our Case 30 sulfapyridine, staphylococcus antitoxin, and a blood transfusion were given, and the patient was clinically practically cured before the growth of organisms from culture of the blood was reported.

SUMMARY AND CONCLUSIONS

1. Staphylococcus septicemia is a condition having a mortality, until very recently, averaging 76 per cent.

2. We are reporting a series of 32 cases with a mortality rate of 44 per cent.

3. As a rule, those cases with an acute and fulminating onset have a higher mortality rate.

4. Of the various types of therapy employed in our series, staphylococcus antitoxin and sulfapyridine gave the most direct evidence of favorably influencing the course of the disease.

5. The last 6 consecutive cases, all in 1939, recovered. All of these received adequate doses of sulfapyridine, and 3 also received staphylococcus antitoxin.

6. There is clinical and experimental evidence to support the tenet that chemotherapy and serotherapy are synergistic in action and that both agents should be used in the treatment of staphylococcus septicemia.

7. Early clinical diagnosis and prompt institution of chemotherapy and serotherapy before corroboration of the diagnosis by blood culture is important.

8. Supportive treatment and sound surgical measures are essential.

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THE INEFFICACY OF LUMBAR PUNCTURE FOR THE REMOVAL OF RED BLOOD CELLS FROM THE CEREBROSPINAL FLUID

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CONSIDERABLE difference of surgical opinion exists as to the value of lumbar puncture for the removal of red blood cells from the subarachnoid space, whether the hemorrhage occurs spontaneously or post-traumatically. The presence of blood in the cerebrospinal fluid has been definitely shown to have pathologic sequellae by the work of Essick,[1] Weed,[2] Bagley,[3] and Wortis,[4] as pointed out by Lehman and Parker.[5] Most observers, such as Bagley,[6] Fay,[7] Keegan,[8] and Sharpe[9] believe that the removal of relatively large amounts of cerebrospinal fluid will eliminate significant quantities of red blood cells, although a few observers raise doubts as to its real value in this respect (Coleman,[10] Dandy[11]).

However, Sprong,[12] in 1934, in a well-controlled study showed, both in the experimental animal (dogs) and in patients, that the rate of disappearance of erythrocytes from the subarachnoid space is not appreciably affected by the withdrawal of cerebrospinal fluid. He injected blood into the cisterna magna of seven dogs and, at varying periods of time thereafter (up to seven days after injection), he removed all the available cerebrospinal fluid by means of a lumbar laminectomy. He found that, after the first forty-eight hours following injection of blood into the cisterna magna, there was never more than 2 per cent of the entire amount of originally injected erythrocytes recoverable, even when all available spinal fluid was removed by lumbar laminectomy, which is a much more complete drainage than is ever accomplished clinically in the treatment of subarachnoid hemorrhage. Russell[13] has also published (1932) curves of the disappearance of red blood cells from the cerebrospinal fluid in clinical cases which exactly correspond to those of Sprong, although he does not relate them to the amount of fluid removed.

It was considered important to verify the experimental work of Sprong as a careful review of the literature to date, following his publication, revealed no similar study. Lehman and Parker[5] stated that Sprong's work, if confirmed, demonstrates the uselessness of a procedure that a majority of surgeons has been assuming to be of major value.

METHODS

A. *Experimental.*—With certain minor variations in technique the work of Sprong was repeated in twice the number of dogs. Food and

Received for publication, May 23, 1940.

TABLE I*

DOG NO.	BLOOD COUNT (MILLION CELLS PER CU. MM.)	C.C. OF BLOOD INJECTED INTO CISTERNA	INTERVAL OF TIME BEFORE DRAINAGE OF ALL CEREBROSPINAL FLUID	C.C. OF CEREBROSPINAL FLUID OBTAINED (LUMBAR LAMINECTOMY)	CEREBROSPINAL FLUID COUNT (R.B.C. PER CU. MM.) (FLUID FROM LUMBAR LAMINECTOMY)	TOTAL NO. OF CELLS INTRODUCED ($\times 10^6$)	TOTAL NO. OF CELLS RECOVERED ($\times 10^6$)	PERCENTAGE OF INJECTED R.B.C. RECOVERED IN CEREBROSPINAL FLUID	PERCENTAGE OF INJECTED R.B.C. WHICH DISAPPEARED SPONTANEOUSLY
1	6,360,000	2 c.c.	2¼ hr.	8.0	500,000	12,720	4,000	31.4	68.6
2	6,000,000	2 c.c.	4 hr.	9.0	355,000	12,000	3,195	26.6	73.4
3	6,840,000	2 c.c.	24 hr.	8.5	330,000	13,680	2,805	20.5	79.5
4	6,480,000	2 c.c.	24.5 hr.	9.7	325,000	12,960	3,153	24.0	76.0
5	5,000,000	2 c.c.	48 hr.	10.5	58,400	10,000	613	6.1	93.9
6	5,390,000	2 c.c.	3 days	7.0	30,200	10,780	211	1.9	98.1
7	6,060,000	2 c.c.	4 days	15.0	1,000	12,120	15	0.12	99.8
8	9,930,000	2 c.c.	5 days	7.3	125,000	19,860	912	4.5	95.5
9	7,440,000	2 c.c.	6 days	10.5	60,000	14,880	630	4.2	95.8
10	6,660,000	2 c.c.	7 days	9.1	55,000	13,320	500	3.7	96.3
11	7,420,000	2 c.c.	8 days	7.4	25,200	14,840	186	1.3	98.7
12	6,270,000	2 c.c.	9 days	7.5	6,800	12,540	51	0.4	99.6
13	7,640,000	2 c.c.	12 days	7.0	40,000	15,280	280	1.8	98.2
14	7,710,000	2 c.c.	21 days	7.5	3,500	15,420	26	0.16	99.84

*Note that the same amount of blood was injected into the cisterna of each dog. After the lapse of forty-eight hours, only 4.5 per cent or less of the red blood cells originally introduced into the cisterna could be recovered by complete subarachnoid drainage (lumbar laminectomy). After the first forty-eight hours practically all the erythrocytes had disappeared spontaneously (see Discussion in text).

water were withheld from the animals during the night preceding experimentation. A series of twenty adult dogs (without choice of breed or sex) was used for the experiments of which six were discarded for technical reasons. Each dog was anesthetized with sodium amytal intraperitoneally (50 mg. per kilogram of body weight) occasionally supplemented with one or two additional injections of 5 mg. per kilogram of body weight each. The same anesthesia was given for the ensuing laminectomy; a small amount of ether vapor (administered by cone) was necessary in a few dogs to insure proper depth of anesthesia. After anesthetization, a cisternal puncture was performed with a No. 20 gauge needle and the cisternal fluid was immediately examined to be certain there were no red cells present due to "needle trauma." Two cubic centimeters of whole blood were removed from a femoral artery and immediately injected into the cisterna magna through the indwelling needle which was then removed. At intervals varying from two and one-quarter hours to twenty-one days after the cisternal injection of blood (Table I), a laminectomy was performed and the tip of the caudal dural sac was doubly ligated with silk sutures and the roots of the cauda equina as well, quite beyond the extensions of the arachnoid around them, to insure the removal of all available fluid. The animal was then placed in the head-up position (80° to 85°) and a small glass tube, a few millimeters larger in bore than the diameter of the dural sac, was utilized for collection of the fluid. The ligated and free dural sac having been introduced into the glass tube, the dura was opened with forceps and scissors a few millimeters from the point of caudal ligation and all available spinal fluid collected by gravity. At the conclusion of the spontaneous flow of fluid from the dural sac, a few cubic centimeters of air were introduced through the small dural opening to displace any additional fluid in the ventricles or basilar cisternae (as in encephalography). Total amounts of fluid varying from 7 to 15 c.c. were thus obtained. The resultant fluid specimens were immediately examined for their individual erythrocyte content and the percentage of originally injected red blood cells recoverable after the various time intervals was computed.

B. *Clinical.*—Two patients with post-traumatic subarachnoid hemorrhage were studied with reference to the value of lumbar puncture in the removal of erythrocytes.

Case 1.—E. W., a colored male, aged 30 years, was admitted to the University of Virginia Hospital (No. 137179) on Jan. 16, 1938, with a diagnosis of concussion and contusion of the brain associated with subarachnoid hemorrhage, following an automobile accident one and one-half hours before admission. Skull x-rays disclosed no fracture. As we were particularly interested at the time in the clinical evidence of disappearance of red blood cells from the spinal fluid in post-traumatic cases which might possibly be attributed to lumbar puncture, a series of five lumbar punc-

tures was done on the patient (Table II), the first one on the day after the injury and the last one nine days after the injury. He left the hospital thirteen days after admission and the injury (Jan. 29, 1938) was clinically well.

TABLE II

CASE I: E. W., AGED 30 YEARS (CEREBRAL CONCUSSION AND CONTUSION, JAN. 16, 1938)*

DATE	INITIAL SPINAL FLUID PRESSURE (MM. OF WATER)	SPINAL FLUID REMOVED	R.B.C. PER CU.MM. IN SPINAL FLUID	PROTEIN
1/17/38†	200	8 c.c.	25,000	----------
1/19/38	130	8 c.c.	2,800	160 mg. %
1/21/38	185	8 c.c.	13,000	100 mg. %
1/23/38	290	4 c.c.	0	75 mg. %
1/25/38	60	5 c.c.	0	50 mg. %
		(very slightly xanthochromic)		

*Patient with post-traumatic subarachnoid hemorrhage. This case demonstrates the futility of lumbar puncture for the effective removal of red blood cells from the spinal fluid, as the great majority of the cells must have disappeared spontaneously (for explanation, see text).

†First lumbar puncture performed twenty-four hours after the hemorrhage.

CASE 2.—A. H., a white girl, aged 5 years, was admitted to the University of Virginia Hospital (No. 138430) on March 13, 1938, immediately after she had been struck by an automobile while walking on the road. She was semiconscious on admission, at which time the diagnosis was concussion and contusion of the brain with probable subarachnoid hemorrhage. For the next three days she remained semiconscious and weakness of the left side developed. Three days after the injury, three cranial burr openings were made to be certain that no massive subdural clot was developing; no such lesion was found but extensive bilateral contusion of the cerebral hemispheres with subarachnoid hemorrhage was demonstrated. She slowly improved and left the hospital thirteen days after the injury (March 26, 1938), at which time she was quite conscious and rational, a definite weakness of the left arm being the only neurologic abnormality. She has been seen in the out-patient department several times since discharge. When last examined, fifteen months after the injury (June 7, 1939), she was in excellent condition with no demonstrable weakness of any extremity.

TABLE III

CASE II: A. H., AGED 5 YEARS (BILATERAL CONTUSION OF THE BRAIN WITH SUBARACHNOID HEMORRHAGE, MARCH 13, 1938)*

DATE	INITIAL SPINAL FLUID PRESSURE (MM. OF WATER)	SPINAL FLUID REMOVED	R.B.C. PER CU.MM. IN SPINAL FLUID	PROTEIN
3/14/38†	70	8 c.c.	70,000	240 mg. %
3/16/38	60	4 c.c.	40,000	60 mg. %
Bilateral superior temporal burr openings (3 in all) made immediately after second lumbar puncture (3/16/38), to rule out subdural bleeding; bilateral contusion of the brain and subarachnoid hemorrhage found				
3/18/38	50	4 c.c.	1,910	50 mg. %

*Patient with post-traumatic subarachnoid hemorrhage. Note that even after three burr openings had been made in the skull, the dura opened and the right lateral ventricle punctured (March 16, 1938) in a patient with massive bilateral cerebral contusion and subarachnoid hemorrhage, it was found (two days after these procedures) that there was a marked reduction in red blood cell content of the spinal fluid (March 16, 1938, compared to March 18, 1938). (For explanation see text).

†First lumbar puncture performed twenty-four hours after the hemorrhage.

A series of three lumbar punctures (including the period before and after the burr openings) was performed on this patient (Table III).

One patient with spontaneous subarachnoid hemorrhage was also studied:

CASE 3.—P. R., a white male (University of Virginia Hospital No. 140192), aged 46 years, developed a spontaneous subarachnoid hemorrhage while driving his car on a long cross-country motor trip. On admission to the hospital (May 28, 1938) on the day of the hemorrhage, the patient was semiconscious and irrational. There was marked photophobia and cervical rigidity. A lumbar puncture was performed the day after admission (Table IV) and subsequently was repeated five times before the patient's discharge. He left the hospital clinically well eighteen days after admistion and to the best of our knowledge has been in good health ever since, leading a sedentary life.

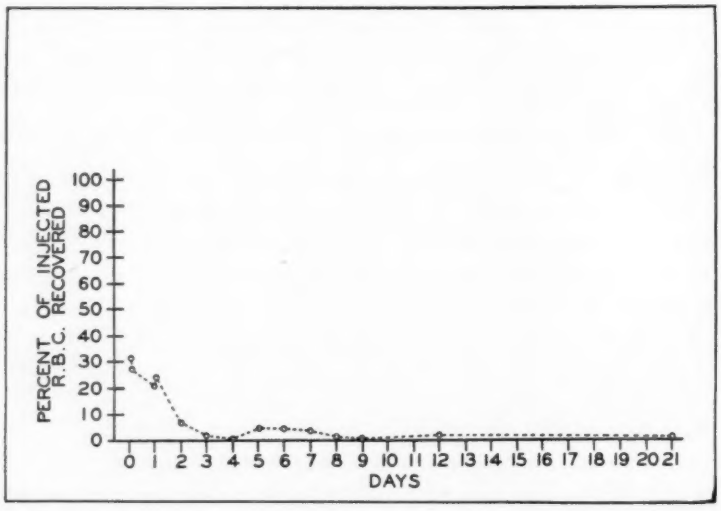

Fig. 1.—Composite curve showing the rate of cerebrospinal fluid clearance in a series of fourteen dogs in which all of the cerebrospinal fluid was withdrawn at various time intervals following the introduction of measured amounts of blood into the cisterna magna (subarachnoid space).

RESULTS

A. *Experimental.*—The animal experiments confirm, in the main, Sprong's results (Table I and Fig. 1). Even following the removal of all available spinal fluid, it is demonstrated (Table I) that, after the first forty-eight-hour period following the injection of blood into the cisterna magna, there was never more than 4.5 per cent of the original number of erythrocytes recoverable and in most instances considerably less (1+ per cent or less). Even after such a short time interval as two and one-quarter hours, only 31.4 per cent of the erythrocytes originally introduced into the cisterna magna were recoverable by complete lumbar drainage. The curve in Fig. 1 shows the sharp drop in recoverable red blood cells after the second day following their introduction into the dog's cisterna magna. The remainder of the red blood cells must be accounted for by spontaneous disappearance, which fraction in the experiments carried out was never less than 95.5 per

cent after the first forty-eight hours. It should be emphasized that no spinal fluid was removed at any time, following the introduction of the blood into the cisterna magna, until the laminectomy was performed for the complete removal of the spinal fluid at periods varying from two and one-quarter hours to twenty-one days after the injection of blood.

B. *Clinical.*—An inspection of the data in Case 1 (Table II) shows that the lumbar punctures undoubtedly had little or nothing to do with the rapid disappearance of erythrocytes from the spinal fluid (see Discussion). One week after the injury (Jan. 23, 1938) no red blood cells were seen in the spinal fluid although only a total of 24 c.c. of fluid had been removed in the three previous punctures.

TABLE IV

CASE 3: P. R., AGED 46 YEARS (SPONTANEOUS SUBARACHNOID HEMORRHAGE, MAY 28, 1938)*

DATE	INITIAL SPINAL FLUID PRESSURE (MM. OF WATER)	SPINAL FLUID REMOVED	R.B.C. PER CU.MM. IN SPINAL FLUID	PROTEIN
5/29/38†	70	7 c.c.	579,000	300 mg. %
5/31/38	120	5 c.c.	200,700	----------
6/ 2/38	210	15 c.c.	4,800	60 mg. %
6/ 5/38	90	5 c.c.	103	60 mg. %
6/ 8/38	98	6 c.c.	621	75 mg. %
6/11/38	115	6 c.c.	33	50 mg. %

*Patient with spontaneous subarachnoid hemorrhage. Note that with the removal of only 12 c.c. of quite bloody spinal fluid (first and second lumbar punctures) the red blood cell content dropped to 4,800 per cu.mm. on the fifth day after the hemorrhage. Obviously, the removal of such a small amount of bloody fluid had little or nothing to do with such a great reduction; spontaneous disappearance must account for almost all of the erythrocytes (see Discussion in text).

†First lumbar puncture performed twenty-four hours after the hemorrhage.

In Case 2 (Table III) it is interesting to note that the third and final lumbar puncture was performed only two days after three burr openings of the skull had been made, with bilateral opening of the dura and tapping of a lateral ventricle. Even with this additional source of red blood cells in the cerebrospinal fluid, there was a marked reduction in erythrocyte content compared to the puncture performed immediately before the burr openings were made (1,910 R.B.C. per cubic millimeter compared with 40,000).

In Case 3 (Table IV), an instance of spontaneous subarachnoid hemorrhage, a lumbar puncture performed the day after admission showed 579,000 R.B.C. per cubic millimeter in the spinal fluid. Five subsequent punctures (the largest amount of fluid removed at any one time was 15 c.c.) in the ensuing thirteen days showed a rapid fall in red blood cell content (especially afer the third day following the hemorrhage).

The data in Tables II, III, and IV clearly demonstrate that most of the erythrocytes in spontaneous or post-traumatic subarachnoid hemorrhage disappear spontaneously. Case 1 (Table II), an instance of post-

traumatic subarachnoid hemorrhage, may be used as an example, especially applicable for computation as the red blood cells had entirely disappeared from the spinal fluid by the seventh day (Jan. 23, 1938) after the injury. If one arbitrarily assumes that the total amount of cerebrospinal fluid present in this adult patient at any one time was 120 c.c., it is seen that on the day after injury there were $3{,}000(\times 10^6)$ red blood cells in the spinal fluid $(25{,}000 \times 1{,}000 \times 120)$. The total number of red blood cells removed at the first puncture was $200(\times 10^6)$, at the second puncture $20.4(\times 10^6)$ and at the third puncture $104(\times 10^6)$, making a total of $324.4(\times 10^6)$ red blood cells removed in the first three lumbar punctures. Thus it is evident that the total number of erythrocytes removed by the three lumbar punctures compared to the total number present on the day after injury constituted only 10.8 per cent of the total $\left(\frac{324.4}{3{,}000.0} = 10.8 \text{ per cent}\right)$. When it is recalled that the first computation of the total number of red blood cells in the cerebrospinal fluid in this patient (as in the other two clinical cases) was made twenty-four hours after the injury (during which interval innumerable red blood cells must have disappeared spontaneously), it is apparent that well over 90 per cent of the erythrocytes must have disappeared spontaneously in this patient (Case 1) within one week (Jan. 23, 1938) of the injury, if not before.

Considering the case of spontaneous subarachnoid hemorrhage (Case 3, Table IV), the results are even more striking. On the basis of the red blood cell count in the spinal fluid on the day after the hemorrhage (579,000 per cubic millimeter) there were $69{,}480(\times 10^6)$ red blood cells present, if one allow 120 c.c. as the total amount of cerebrospinal fluid present, an average figure for an adult patient. Six lumbar punctures were carried out on the patient; the total number of red blood cells removed in the six punctures was calculated as $5{,}133.4(\times 10^6)$. It is seen, therefore, that the total number of erythrocytes removed by all the punctures, compared to the total number present on the day after the hemorrhage, constituted but 7.4 per cent of the total $\left(\frac{5{,}133.4}{69{,}480} = 7.4 \text{ per cent}\right)$, so that 92.6 per cent of the red blood cells must have disappeared spontaneously after the first twenty-four hours following the hemorrhage, in addition to the red blood cells that were undoubtedly hemolyzed or otherwise eliminated from free circulation in the cerebrospinal fluid during the first twenty-four hours following the intracranial vascular accident, during which latter period no lumbar puncture was performed.

DISCUSSION

The experimental work is more analogous to spontaneous subarachnoid hemorrhage than it is to the post-traumatic variety, as no parenchymatous brain injury was induced.

It is demonstrated that, following the first forty-eight hours after the introduction of a measured amount of blood into the dog's cisterna magna, only 4.5 per cent or less of the erythrocytes introduced could be recovered by complete subarachnoid drainage (lumbar laminectomy). After the first forty-eight hours, nearly all the red blood cells had disappeared spontaneously. The slightly greater number of erythrocytes recoverable in Dogs 8, 9, and 10 (Table I) than in Dogs 6 and 7 may be explained on the basis of possible continued oozing (as in clinical cases) in the former dogs. Even with this possibility, it is apparent that the average lumbar puncture, as performed clinically, removes few red blood cells, relatively or absolutely. Thus these experiments substantiate the opinion that, so far as removal of erythrocytes is concerned, lumbar puncture is of slight value, as spontaneous disappearance undoubtedly eliminates most of the red blood cells, especially after the first forty-eight hours.

The experiments described above were not devised nor were they expected to explain by what process or processes the erythrocytes disappeared from the subarachnoid space, but they do demonstrate the relative futility of lumbar puncture for their removal. The red blood cells are not entirely eliminated by hemolysis, although this is perhaps the most important process accounting for their disappearance. It must be recalled, however, that Essick[1] in 1920 demonstrated that arachnoid cells are capable under certain conditions of becoming phagocytes and Bagley[14] has clearly shown in the experimental animal that, when blood is introduced into the subarachnoid space, certain of the arachnoid (phagocytic) cells become filled with blood pigment resulting from the engulfment of erythrocytes. He also showed that the pigment-laden cells are found even in the chronic stage of meningeal thickening secondary to the injection of blood into the cisterna magna or elsewhere in the subarachnoid space. Furthermore, all surgeons and pathologists who have seen considerable numbers of brains that had been subjected to trauma or following spontaneous subarachnoid hemorrhage are familiar with the fact that blood becomes agglutinated in the subarachnoid spaces over the cerebral convexities and in the basilar cisternae with great frequency; by this sequel to subarachnoid hemorrhage still more erythrocytes become enmeshed and are incapable of removal by lumbar puncture. It is probable that these three processes: (a) hemolysis, (b) phagocytosis by arachnoid cells, and (c) enmeshment and agglutination of intact erythrocytes in the subarachnoid space account for the major portion, if not the entire number, of red blood cells that disappear spontaneously from the cerebrospinal fluid after subarachnoid hemorrhage.

A plea is made for reduction of the frequency of lumbar puncture in cases of subarachnoid bleeding. At the present time in this clinic such punctures are infrequently performed in post-traumatic and in

spontaneous subarachnoid hemorrhage. In a previous communication from this clinic[15] it was reported (1938) that lumbar puncture was performed in only 15 per cent of all head injury cases. This has been confirmed by a more recent analysis (1940) of 391 additional cases (consecutive admissions) of all types of head injury in which lumbar puncture was performed in 15.3 per cent of all cases.[16] Dandy[17] considers it of little or no use in any post-traumatic case.

It is still rather widely believed that lumbar puncture should be frequently performed in cases of spontaneous and post-traumatic subarachnoid hemorrhage. This is apparent from a review of the literature of the last few years in regard to spontaneous subarachnoid hemorrhage alone. To refer to only a few of the many recent writers on this subject: Leary and Myerson[18] in 1931; Blackford,[19] Strauss, Globus, and Ginsburg,[20] and Ohler and Hurwitz[21] in 1932; Hyland[22] and Osterman[23] in 1933; and Eley[24] and Waite[25] in 1934; all recommended lumbar punctures with removal of rather large amounts of spinal fluid until it becomes clear. Many other writers could be quoted with similar views. Also, the same viewpoint is widespread among the profession in regard to post-traumatic subarachnoid hemorrhage.

It appears that these views are, for the most part, without sound physiologic or pathologic foundation for reasons previously stated. They are certainly not borne out by the experimental data (reported herewith) having to do with the spontaneous disappearance of red blood cells from the spinal fluid. We are inclined to agree with the opinion of Hall,[26] who, in discussing spontaneous subarachnoid hemorrhage, prefers lumbar puncture initially for diagnosis and subsequently only to relieve signs of medullary compression such as respiratory distress, bradycardia, and stupor, for which purpose it is probably justified. The same statement holds true for occasional post-traumatic cases in which one is certain that there is no massive sub- or extradural clot, either from the clinical signs or by previous operation.

CONCLUSIONS

1. Experimental and clinical evidence is presented to demonstrate that lumbar puncture, when used for the removal of red blood cells from the subarachnoid space, is almost completely ineffective.

2. This fact, not generally known and accepted, should be more universally applied to clinical cases; i.e., lumbar punctures should not be done for the sole purpose of removing erythrocytes from the subarachnoid space.

The writer wishes gratefully to acknowledge the suggestions and advice of Dr. E. P. Lehman in the present study. Dr. William Bray, Director of Clinical Laboratories at the University of Virginia, kindly granted all facilities required for the necessary laboratory calculations.

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ABSORPTION OF SULFANILAMIDE FROM BURNED SURFACES

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THE tendency of burns to become infected with streptococci[1] and the success which has attended the use of sulfanilamide locally in compound fractures[2] and other forms of trauma caused us to make these observations on the effect of sprinkling the dry powder on small areas in eight cases of burns. The rapidity of absorption and the high blood levels obtained in several cases were so striking that we are making this report to call attention to the probable value of this method of administering sulfanilamide prophylactically and therapeutically, and incidentally to add evidence in the debated question of whether or not there is considerable absorption of diffusible material from burned skin.

The work of Underhill, Kapsinow, and Fisk[3] has often been cited as opposing the so-called toxic theory of the cause of death from burns. They showed that when phenolsulphonephthalein or strychnine was injected into burned areas, its absorption was distinctly inhibited. One might infer, therefore, that it is unlikely that any hypothetical toxic substance would be taken up by the blood stream and distributed to other parts of the body.

Mason, Paxton, and Shoemaker[4] found that potassium iodide was readily absorbed from burned areas. Mitchiner[5] states that Petit and Lister employed perchloride of mercury in the treatment of burns in the nineteenth century, with the idea of precipitating the surface proteins. It is said that all of the patients so treated died or suffered severely from mercurial poisoning. Recently, Arnaud[6] reported his experience with the treatment of nine cases of burns with mercurochrome dressings. Nephritis and other symptoms of mercurial poisoning developed, and mercury was detected in the urine in twenty-four hours. In a comment on this article, Graham[7] aptly warns against any further use of mercurochrome in the treatment of burns. To these instances of active absorption from burned surfaces, we add the following data with regard to sulfanilamide.

CASE REPORTS

CASE 1.—M. W., a 24-year-old white woman, suffered second degree burns of the arms and face in a blowtorch explosion. Two hours after the injury, sulfanilamide powder was applied to the extensor surface of the left forearm, the area measuring

Received for publication, July 7, 1940.

Fig. 1.—Showing sulfanilamide powder applied to the forearm of patient in Case 1. The photograph was taken two and one-half days after the initial application. The ruler parallel to the forearm is in centimeters.

Fig. 2.—Showing sulfanilamide powder applied to the hand of patient in Case 2. The photograph was taken two and one-half days after the initial application. The ruler parallel to the hand is in centimeters.

15 cm. by 4 cm. (Fig. 1). Approximately 5 Gm. of powder was applied initially, and small amounts were sprinkled on at intervals thereafter, making a total of about 40 Gm. being applied over a period of three and one-half days. The curve of the blood sulfanilamide level is shown in Fig. 3. A level of 9.4 mg. was obtained. No infection developed in this area or in the other areas which had been treated with tannic acid jelly.[8]

CASE 2.—D. W., a 29-year-old white man, received burns of the hands and face in the same explosion in which the patient in Case 1 was burned. Two hours after the accident, sulfanilamide powder was applied to an area measuring 8 cm. by 6 cm. on the back of the left hand (Fig. 2), approximately 30 Gm. of powder being used altogether. A blood level of 7.8 mg. was reached on the third day. Healing was rapid and uneventful.

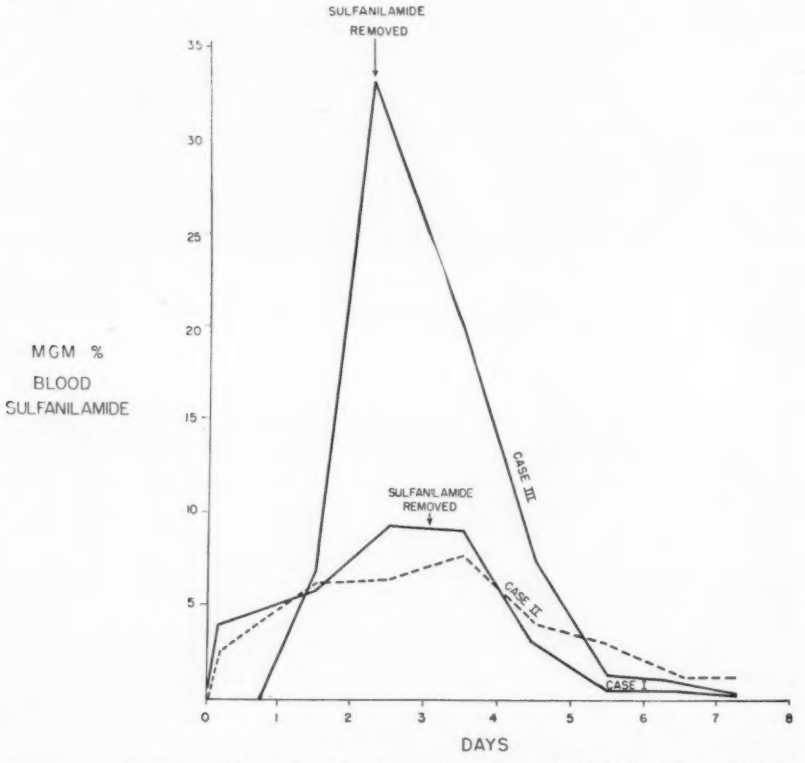

Fig. 3.—Curves showing the rate of absorption of sulfanilamide from the burned areas in Cases 1, 2, and 3.

CASE 3.—M. K., a 38-year-old white man, sustained a third degree burn of the left leg in a gasoline fire. Primary treatment was with tannic acid jelly. Infection developed under the eschar, and it was removed; cultures showed *Bact. pyocyaneus* and nonhemolytic streptococci. Sulfanilamide powder was sprinkled on the leg over an estimated area of nearly 30 by 60 cm. Approximately 60 Gm. of the powder was used altogether. The next morning the patient was put in a tub bath, and afterward more powder was put on. He became cyanotic and confused. The blood sulfanilamide level was 33 mg. The remainder of the powder on the leg was removed by irrigation. Treatment of the infected granulating surface was continued with daily brine baths, and split grafts were applied early.

Isolated observations were made on five additional cases (Table I).

TABLE I

CASE NO.	SIZE OF AREA	LEVEL OF BLOOD SULFANILAMIDE	NO. DAYS INTERVENING
4	4 by 5 cm.	2.3 mg.	4
5	5 by 6 cm.	4.5 mg.	3
6	3 by 4 cm.	1.0 mg.	6
7	4 by 5 cm.	1.2 mg.	5
8	6 by 3 cm.	2.0 mg.	2

DISCUSSION AND CONCLUSIONS

In presenting this report, it is not our intention to advise the widespread use of sulfanilamide powder in the treatment of burns. In fact, our experience with putting the powder on very small areas indicates that there is danger of overdosage if the drug is used indiscriminately on larger areas. It would appear to be a useful procedure in the case of a large infected burn to put the powder on a small portion and to obtain the desired blood level by this route rather than by giving the drug by mouth. Nausea and vomiting are common enough in burns without the additional factor of chemotherapy by mouth. It is possible that further experience will produce a technique whereby the drug can be used routinely in a prophylactic manner to prevent secondary streptococcic infection.

This experience is additional evidence against the view that burned tissues form a poor absorbing surface.

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PEPTIC ULCER AND DIARRHEA FOLLOWING THE REMOVAL OF THE PREVERTEBRAL GANGLIA IN DOGS

The Antispasmodic Effects of Magnesium Sulfate, Pentobarbital, and Atropine Sulfate

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THE close association of psychic disturbances and diarrhea is well known to the clinician. Although the mechanism involved is not understood, there is experimental evidence which points to a sympathetic-parasympathetic imbalance as a very important factor. Popielski[1] reported his experience with removal of the celiac and superior mesenteric ganglia in twenty-two dogs. After operation all of the animals developed watery diarrhea and passed both mucus and bright red blood in the stools. Two animals died nine and twenty-five days after ganglionectomy from the inanition attending the severe diarrhea. In the animals that survived over a two-week period, it was usually found that the blood and mucus disappeared from the stools and diarrhea alternated with formed feces. Complete protocols were given for the autopsy of five animals and in all of these ulcers were found in the stomach and duodenum. Other changes noted were marked hyperemia and hemorrhagic erosions along the gastrointestinal tract.

Laignel-Lavastine[2] wrote a comprehensive review of the celiac plexus and its function. He concluded from his experiments on complete removal that this plexus exerts a restraining action on the movements of the intestine, hence the bloody dejecta and diarrhea which are noted after ablation.

Vedova[3] removed the right and left celiac ganglia in dogs and also injected alcohol into the plexus. No mention is made of diarrhea after such procedures. Donati[4] removed only the left celiac ganglion in dogs without a disturbance of bowel activity. Grundelfinger[5] excised both celiac ganglia and does not report any disturbance in the frequency of bowel movements. The absence of diarrhea in these experiments may well be due to the incomplete removal of the prevertebral ganglia, for in the experiments of Popielski and Laignel-Lavastine the superior mesenteric ganglia were also excised. Donati[4] and Peiper[6] make no reference to diarrhea after the removal of the celiac plexus in rabbits.

The implications of the findings by Popielski and Laignel-Lavastine are of sufficient importance to reconsider carefully. They suggest that

Received for publication, July 8, 1940.

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in dogs a radical removal of the celiac plexus will effect a marked diarrhea. In addition to repeating their work, the present experiments include a study of the effect of this operation upon rectal tonus and motility. The influence of certain drugs on the increased rectal contractions was tested after ganglionectomy. The operative procedure used by other investigators was enlarged to include removal of the inferior mesenteric ganglion, which lies quite apart from the celiac plexus. *Subsequently in this paper, the term prevertebral ganglionectomy will be used to denote the removal of the right and left celiac ganglia, the superior and inferior mesenteric ganglia.*

METHODS

Male and female dogs of medium size were used. They were fed on a diet of boiled meat and pasteurized milk throughout the experiment. During the three days preceding the operation, the stools were examined carefully for gross evidence of blood and mucus.

Studies were made of rectal contractions in all of the animals at two- or three-day intervals before and after operation. For this purpose a small balloon attached to a catheter was inserted by means of a forceps through a proctoscope in the rectum. The balloon was placed two inches above the anus and the protoscope withdrawn. After connecting the balloon to a mercury manometer, 40 c.c. of air were introduced slowly through a sidearm in the system. A record of the contractions was made over a period of fifteen to twenty minutes with a writing arm recording the oscillation of the mercury on a smoked drum. In each study a record was made of the pressure within the balloon when it was filled with 40 c.c. of air, outside the animal (Fig. 1).

After it had been established that increased rectal contractions were present after prevertebral ganglionectomy, the influence of intravenous pentobarbital, $MgSO_4$, or atropine sulfate was tested in various animals. Throughout the work with the balloon, no difficulty was encountered in obtaining records which were free from the elevation which occurs when the animals move or strain.

For the operative procedure ether anesthesia and sterile technique were used. Through a midline abdominal incision the inferior mesenteric, superior mesenteric, and celiac ganglia were removed. In all of the animals the celiac, superior, and inferior mesenteric arteries were cleaned of nerve tissue for a distance of 2 cm.

A preliminary control operation was performed ten days before removal of the ganglia in two animals. The abdomen was opened and retraction of the intestines was maintained for one hour so that all of the trauma except the actual excision of the nerves was duplicated. The animals were subsequently studied with the rectal balloon and one week later were subjected to ganglionectomy.

In two other animals the abdomen was opened under ether and the intestines retracted as for ganglionectomy over a one-hour period. One

Fig. 1. Fig. 2. Fig. 3. Fig. 4.

Figs. 1-4.—Rectal contractions from Animal 8. They show that simple laparotomy with retraction of the intestines is not responsible for the increased contractions. Subsequent ganglionectomy in such an animal elicits the increment in rectal activity as noted in all nine animals examined. Each figure represents a three-minute period. The lowest line is the base; the middle line is the balloon containing 40 c.c. of air outside the animal; the upper line is the balloon in the rectum. Recording is by mercury manometer, and pressure exerted is twice the height of the record. Fig. 1, Animal 8, before operation; Fig. 2, one week after simple laparotomy; Fig. 3, day after prevertebral ganglionectomy; Fig. 4, one week after prevertebral ganglionectomy.

week later they were sacrificed for examination of the gastrointestinal tract. In sacrificing animals, they were first etherized, the abdomen was opened, and the entire gastrointestinal canal excised and opened. The whole specimen was preserved in 10 per cent formalin and at a later date microscopic slides were prepared of the abnormal areas. These were stained with hematoxylin and eosin.

RESULTS

In all but two of the animals, formed stools were passed during the three days before operation. These two had mushy, unformed stools, which was attributed to the use of horse meat in their diet. No animal in this series showed gross blood or mucus in the stools preoperatively. All four dogs subjected to simple laparotomy had formed stools after this operation.

The studies with the balloon before operation showed uniform results in all animals. Figs. 1 and 5 are typical curves.

Table I gives the survival period and autopsy findings in the nine animals subjected to ganglionectomy. Animals 1 and 2 survived less than four days. One of these animals suffered peritonitis in the left upper quadrant of the abdomen from a perforated gastric ulcer; the other had an intussusception of the terminal ileum through the ileocecal valve with gangrene and peritonitis.

Animals 3 and 4 were sacrificed at a time when they could only survive a period of hours, to judge by their weakened condition. They suffered severe weight loss despite a good appetite and lost so much strength that they could not eat or even stand up toward the end. The diarrhea in these animals was so acute that they soiled themselves badly and had ulcers and erosions of the skin where the digestive juices had been deposited.

The remaining animals withstood the operation quite well and might have survived indefinitely had they not been sacrificed for examination of the gastrointestinal tract.

In all nine animals subjected to ganglionectomy the following results were observed:

1. *Diarrhea.*—This became evident as soon as the animals regained consciousness. The discharge consisted of mahogany colored liquid with large amounts of mucus. When the animals commenced to eat, undigested food would appear in the feces. Animal 4 drank some milk forty-eight hours after operation, and in fifteen minutes passed bile-stained milk curds by anus. Characteristic of the feces was a powerful stench, as has also been noted by other investigators. The diarrhea was most pronounced during the first ten days after operation. If the animals were able to survive this time in a fair state of nutrition, the diarrhea lessened and the undigested meat particles disappeared from the feces. The stools were unformed in all but one of the surviving

TABLE I

SUMMARY OF PATHOLOGIC FINDINGS IN 9 DOGS SUBJECTED TO CELIAC GANGLIONECTOMY

ANIMAL	POST-OPERATIVE DAY OF DEATH	CAUSE OF DEATH	CONDITION AT DEATH	FINDINGS AT AUTOPSY
1.	3	Peritonitis	Severe diarrhea; blood in stools	Peritonitis localized to left upper quadrant; perforated ulcer on greater curvature of stomach; three ulcers (0.4 to 0.8 cm. wide) on the lesser curvature; dark blood throughout the entire gut and marked hyperemia of mucosa
2.	3	Peritonitis	Severe diarrhea; blood in stools	Intussusception of terminal 20 cm. of ileum through ileocecal valve with gangrene of terminal ileum and peritonitis; stomach spastic with multiple intramucosal hemorrhages and erosions; these changes most marked on tips of rugae; marked duodenitis and hyperemia of entire gut
3.	14	Too weak to eat; killed under ether	Marked loss of weight; severe diarrhea; multiple ulcers of skin where feces had touched	Marked edema of entire gut; two ulcers over pyloric ring (0.4 by 0.2 cm. and 0.3 by 0.1 cm.) with red edges; intramucosal hemorrhages in cecum running at tips of rugae in a transverse linear pattern; pyloric ulcers, on section, invaded the muscularis mucosa
4.	12	Too weak to eat; killed under ether	Same as Animal 3	Edema of entire gut; marked duodenitis both grossly and microscopically; two superficial erosions 0.6 cm. wide at junction of ileum and jejunum; lower half of colon showed marked hyperemia; intramucosal hemorrhages of ileocecal valve
5.	2 mo.	Killed under ether	Good health; formed stools alternating with mushy; all stools tarry black	Marked edema of entire gut; at junction of jejunum and ileum was a 1 by 0.8 cm. firm, white scar extending through entire wall of gut; sections showed muscle occupied largely by fibrous tissue and a thin layer of epithelium without villi; for 30 cm. below this scar the mucous membrane was markedly hyperemic both grossly and microscopically; lumen of gut contained old blood and on section many intramucosal hemorrhages were seen

TABLE I—CONT'D

ANIMAL	POST-OPERATIVE DAY OF DEATH	CAUSE OF DEATH	CONDITION AT DEATH	FINDINGS AT AUTOPSY
6.	24	Killed under ether	Good health; holding weight; two or three watery stools a day	Edema of entire gut; nothing abnormal either grossly or microscopically save for edema
7.	7	Killed under ether	Watery stools with mucus and flecks of red blood; undigested food in feces	Edema of entire gut; three (0.5 by 0.3 cm.) ulcers of lesser curvature; 0.3 cm. wide ulcer crater in fundus with rugae converging on it; 5 by 2 cm. area of ulceration and erosion along greater curvature; intramucosal hemorrhages of ileocecal valve; section of gastric ulcers showed destruction of muscularis mucosa with atypical epithelium at edge of ulcer; considerable scar tissue in base of ulcer
8.	7		Watery stools with mucus and flecks of red blood; undigested food in feces	Entire gut edematous; intramucosal hemorrhages on tips of rugae in cecum; intramucosal hemorrhages of ileo cecal valve
9.	10		Loose, watery stools, four to six daily	Gastric ulcer, 1 cm. wide, over middle of greater curvature of stomach; 0.5 cm. wide ulcer with red edges 15 cm. above ileocecal valve; this was almost perforated; intramucosal hemorrhages of ileocecal valve; hyperemia of colon, most marked in cecum, with some intermucosal hemorrhages microscopically

animals during the period of observation. The exception, Animal 5, had three or four mushy stools a day alternating with formed stools two months after ganglionectomy. Animal 6 continued to have watery feces with mucus twenty-four days after operation.

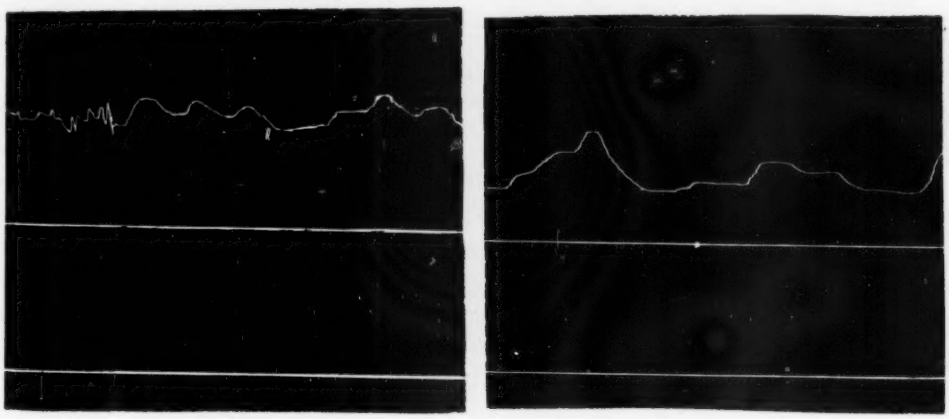
2. *Mucus.*—Gross amounts of mucus are not normally present in dog's feces, but, after removing the celiac, superior and inferior mesenteric ganglia, large particles of mucus were present in each dejection. At times long strips of mucus were passed, and these appeared to be casts of the colon. The amount of mucus diminished as the diarrhea subsided.

3. *Bloody Stools.*—All animals passed blood in the feces after ganglionectomy. In three of the dogs this amounted to 1 dr. or more on several occasions, but in the others only blood-stained mucus was passed.

Fig. 5. Fig. 6. Fig. 7. Fig. 8.

Figs. 5-8.—From Animal 4 which succumbed from the severe diarrhea following prevertebral ganglionectomy. Note the increase in rectal activity with time. Each figure is a three-minute interval of rectal contractions. Fig. 5, Animal 4, preoperatively; Fig. 6, eighteen hours after operation; Fig. 7, five days after operation; Fig. 8, nine days after operation.

Tenesmus and straining were invariably associated with the appearance of blood. The animal would defecate watery feces after which it continued to strain for several minutes. Thick mucus was then expressed followed by blood-tinged mucus. If the tenesmus continued even longer, a drop or two of bright red blood would be passed. The blood disappeared as the diarrhea subsided. It is assumed that the blood passed at the end of defecation came from the lower gut. Whether changed blood from higher up in the intestinal canal was also present in the feces cannot be stated with certainty. Suggestive evidence in favor of this was furnished by Animal 5. Over a two-month period this animal passed black stools when other animals in the colony had dark brown stools on the same diet. At autopsy a 30 cm. segment of ileum was found to be markedly inflamed and to contain bloody fluid. Microscopic section of this area showed widely dilated blood vessels in the villi and intramucosal hemorrhages.



A. *B.*

Fig. 9.—The increased rectal contractions are still present as long as twenty-four days and two months after prevertebral ganglionectomy. *A*, Animal 6, rectal contractions twenty-four days after ganglionectomy; *B*, Animal 5, rectal contractions two months after ganglionectomy.

4. *Increased Rectal Contractions.*—All nine animals subjected to ganglionectomy were studied with the balloon catheter before and after operation. There were none or only occasional slight contractions before operation (Figs. 1 and 5). Whereas there were individual differences, all animals showed increased rectal activity after ganglionectomy. In most animals this was greatest on the first few days after operation, and the balloon was often defecated soon after insertion. In the two that succumbed from the effects of the severe diarrhea there was a gradual increase in response with the maximum reached just before death (Figs. 5-8). In no animal studied did the rectal response return to the normal preoperative level. One animal was studied two months and another twenty-four days after operation (Fig. 9 *A* and *B*). In the four control animals there was no essential difference between the preoperative

studies with the balloon and those after simple laparotomy. The two control animals subjected to ganglionectomy had the same increase in rectal contractions as the other dogs. (Figs. 1-4.)

During the preoperative period two of the animals had a watery diarrhea caused by the eating of some horse meat. Rectal irritability was studied during this period and showed no essential difference in the curves from the normal.

Necropsy Findings.—Table I gives in summary form the findings at autopsy. Satisfactory microscopic studies were not available in Animals 1 and 2 which died during the night. These animals were the only ones to show marked hyperemia of the entire gut grossly. In the others the hyperemia was localized. Four of the nine animals showed peptic ulcers. Two of these had discrete ulcers on both greater and lesser gastric curvatures (Animals 1 and 7). Animal 7 had also a 5 by 2 cm. area of irregular ulceration along the greater curvature and an acute ulcer in the lower ileum which had almost perforated. Animal 9 had a 1 cm. wide ulcer on the greater curvature toward which the rugae converged. Animal 3 showed two acute ulcers directly overlying the pylorus. On microscopic study of the lesions in Animals 3, 7 and 9, the ulcers were found to extend beneath the muscularis mucosa. There was an acute inflammatory reaction throughout the base and at the edges atypical epithelium was found and regeneration appeared to be in progress.

Animal 2 had a marked gastritis with intramucosal hemorrhages along the tips of the rugae, and Animal 4 showed a severe duodenitis. Animal 5, which was sacrificed two months after ganglionectomy, had a white scar at the junction of the ileum which was covered with a thin layer of epithelium without villi. Five animals showed gross interstitial hemorrhages in the mucosa overlying the ileocecal valve. There were no ulcerations or gross erosions observed in the colon, but hyperemia was noted grossly in five animals. The microscopic sections taken from the areas of hyperemia and intramucosal hemorrhage in these animals showed a wide dilatation of capillaries. In small foci, at the superficial border of the mucosa, there appeared hemorrhagic areas which had caused a necrosis of the surrounding tissue and of the overlying epithelium. In other areas there were seen large round cells loaded with hemosiderin where earlier subsurface hemorrhages might well have occurred.

In the two animals subjected to simple laparotomy, no demonstrable abnormalities of the gastrointestinal tract were found.

Inhibition of Rectal Contractions With Drugs.—The animal with its celiac, superior and inferior mesenteric ganglia removed constitutes an excellent test object for antispasmodic agents. Only $MgSO_4$, pentobarbital, and atropine were tested in these animals. They were all given intravenously in large amounts. Atropine sulfate (0.5 mg.) was tested on two, $MgSO_4$ (5 c.c. of 12.5 or 25 per cent solution) on four, and pentobarbital (anesthetic dose) on two animals. In each instance there was

Fig. 10. Fig. 11. Fig. 12. Fig. 13.

Figs. 10-13.—The effect of intravenous calcium gluconate and magnesium sulfate on the rectal contractions after prevertebral ganglionectomy. Calcium gluconate has no effect when given in relatively small doses. Twenty-five per cent magnesium sulfate abolishes the rectal contractions for long periods. The control observations in the two experiments were essentially the same. Calcium gluconate was given on the sixth and magnesium sulfate on the seventh postoperative day. Fig. 10, Control; Fig. 11, immediately after 5 c.c. of 10 per cent calcium gluconate intravenously; Fig. 12, immediately after 5 c.c. of 25 per cent $MgSO_4$ intravenously; Fig. 13, one and three-fourths hours after recording shown in Fig. 12.

Fig. 14. Fig. 15. Fig. 16.

Figs. 14-16.—The effect of intravenous atropine on rectal contractions in Animal 3, six days after prevertebral ganglionectomy. The time intervals are three minutes. Whereas atropine abolishes contractions, it does so only for a short time as compared with magnesium sulfate. Fig. 14, Control in Animal 3, six days after ganglionectomy; Fig. 15, immediately after atropine sulfate, 0.5 mg. intravenously; Fig. 16, one hour after tracing shown in Fig. 15.

Fig. 17. Fig. 18. Fig. 19. Fig. 20.

Figs. 17-20.—The effect of an anesthetic dose of nembutal on the rectal contractions of Dog 5, four days after prevertebral ganglionectomy. All are three-minute intervals and show the prolonged inhibiting effect. Further observations were impossible because the animal was too restless during the early recovery period. Fig. 17, Control; Fig. 18, immediately after anesthetic dose of nembutal intravenously; Fig. 19, one hour after tracing shown in Fig. 18; Fig. 20, two and three-fourths hours after tracing shown in Fig. 18.

an almost immediate cessation of rectal contractions. Figs. 10-20 show the results of these studies. It is to be noted that pentobarbital and $MgSO_4$ have quite a prolonged action in inhibiting contractions; whereas, the action of atropine is over at the end of one hour. A relatively small dose of calcium gluconate given intravenously to one animal failed to inhibit contractions. In another animal it was shown to reverse the inhibiting action of $MgSO_4$.

DISCUSSION

The results obtained in these experiments confirm those of Popielski and others. They indicate that in the dog the celiac, superior and inferior mesenteric ganglia are an essential element in the normal functioning of the gastrointestinal canal and that they exercise a restraining influence on its activities. The watery diarrhea immediately after ganglionectomy when the animals were fasting points to a marked secretory activity of the intestine. This confirms previous observations on the cat by Wright and co-workers[7] where it was shown that the celiac ganglia constitute an important brake on the secretory function of the duodenum and small intestine. That mucus was passed in large amounts is explained by the work of Wright, Jennings, and Florey.[8] These authors demonstrated that the nervi erigens is a powerful secretory nerve; whereas, the postganglionic fibers from the inferior mesenteric ganglion inhibit the secretion of mucus by the colon.

Passage of blood during the days immediately following operation came at the end of defecation and was always associated with tenesmus and straining, which suggests that it was related to spasm of the lower colonic segment. The absence of ulcers and erosions in the colon of animals that passed blood just before death suggests that the blood had its origin in capillary hemorrhage and was related to the intramucosal hemorrhages found at autopsy. In previous communications[9, 10] it has been shown that hemorrhage can be produced from an explant of dog's colon by agents capable of initiating severe spasm. The mechanisms by which spasm produces hemorrhage from the mucosal surface is not clearly understood. Since the blood vessels to the mucosa must traverse the powerful circular and longitudinal muscles of the intestine before reaching their destination, they can be completely occluded when these muscles contract.

Spasm of the intestinal muscles at first may close the exit for the blood through the veins and then through the arteries, thus trapping a large reservoir of blood in the dilated capillary bed of the mucosa. Further spasm may exert such a powerful pressure on the vessels that they rupture, a possible explanation for the erosions and intramucosal hemorrhages seen after inducing spasm by a great number of agents (dysentery toxin,[8] pilocarpine,[11] physostigmine and acetyl choline,[10] and barium chloride[12]). Another possibility is the production of severe anemia by the muscle spasm and a resulting death of the mucosal cells

Studies with the balloon revealed a constant increase in rectal contractions after operation and indicate that the diarrhea was dependent on an increased irritability of the gastrointestinal tract to the normal stimulus of the feces. The absence of such increased contractions during the diarrhea due to horse meat suggests that there are two distinct mechanisms for diarrhea in the dog.

The importance of finding peptic ulcerations in these animals cannot be evaluated without further study. Similar results were noted by Popielski, Laignel-Lavastine, and Grundelfinger. The observations of the last author must be discounted, however, for he considered the normal mucosal depressions in the dog's duodenum as ulcerations. Volini and associates[13] have demonstrated that these apparent defects are actually covered by normal mucosa. Donati found little evidence of mucosal damage in his dogs, but he only resected the left celiac ganglion, a procedure which also yielded negative results in the hands of Grundelfinger. Ivy[14] reported no ulcers in dogs after dividing the splanchnics or removing the celiac plexus.

The effect of stimulating the vagi theoretically should give much the same result as removal of the celiac ganglia. Stahnke[15] observed defects in the mucous membrane over the lesser curvature in two of five dogs that had chronic stimulation of the vagi.

The experiments on rabbits have been contradictory, the same procedure giving quite different results in the hands of various investigators. Hemorrhagic erosions of the stomach have been described both after bilateral vagotomy and resection of the celiac plexus. Others obtained negative results with these procedures. The reader is referred to the work of Talma,[16] Donati,[4] Durante,[17] Van Yzeren,[18] and Alvarez.[19]

In dogs with severe diarrhea emaciation develops rapidly. Weech and Paige[20] have shown that protein deficiency in dogs is often associated with peptic ulcers. Keller[21] autopsied 150 undernourished dogs and found round, hemorrhagic craters in the stomach of ten animals. These considerations make it impossible to say definitely whether inanition or prevertebral ganglionectomy was responsible for the peptic ulcers in these experiments.

The antispasmodic action of pentobarbital as demonstrated in these experiments confirms the previous observations of others on members of the barbiturate group.[22-25] The similar effect of parenteral $MgSO_4$ was first investigated by Meltzer and Auer[26] and more recently by Straub and Schild[27] and Kanda.[28] In our experiments these agents evidenced an antispasmodic action of at least two hours. The antispasmodic action of these two agents has been shown to be a peripheral one (26, Mg; and 23, pentobarbital).

Clinical Implications.—The finding of diarrhea and mucus in the animals subjected to prevertebral ganglionectomy has a bearing on so-called mucus colitis. Jones and White[29] call attention to the neurogenic factors

in this disorder and to the fact that parasympathetic stimulation reproduces the essential elements of the disease. The experiments here reported suggest that underactivity or lack of sympathetic control to the colon may well lead to the same result as actual parasympathetic stimulation of that organ.

The association of tenesmus with rectal bleeding in these experiments has a bearing on one aspect of ulcerative colitis. On careful questioning one can invariably elicit the story that the patients know beforehand when blood will appear in the stools. Severe lower abdominal cramps, tenesmus, and a dull or sharp ache in the rectum preface the appearance of blood. These are all symptoms associated with severe muscle contraction.

The efficient antispasmodic action of pentobarbital and $MgSO_4$ suggests their use in clinical conditions associated with severe muscle spasm such as acute ulcerative colitis.[39]

SUMMARY

1. When the celiac and superior and inferior mesenteric ganglia are removed in dogs there result a foul diarrhea, with mucus and blood in the stools and increased rectal activity as measured with a balloon.

2. At autopsy four of nine animals subjected to this operation showed peptic ulcers, one of which had perforated. These ulcers may be due to inanition rather than the ganglionectomy.

3. Other changes noted were intussusception, gastritis, duodenitis, enteritis, hyperemia, edema of the intestine, and intramucosal hemorrhages. A possible explanation for the appearance of these lesions has been offered.

4. It was shown that $MgSO_4$, pentobarbital, and atropine all relax the colon when given intravenously in large doses; calcium does not, but reverses the effect of magnesium.

5. The relationship of these findings to various clinical problems has been discussed.

The author appreciates the suggestions and help offered by Dr. Walter B. Cannon and Dr. Joseph C. Aub. Thomas Barnett gave valuable technical assistance.

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LARGE ISLET-CELL TUMOR OF THE PANCREAS

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THE successful excision of islet-cell tumors of the pancreas has now been accomplished with sufficient frequency to render perhaps unwarranted the report of a single rather typical case. Whipple and Frantz[1] have reviewed the literature up to 1935 and in a more recent summary Whipple[2] states that he has collected 110 cases (including 15 cases of his own) of hypoglycemia with pathologically proved islet-cell tumors. Eighty-two were removed by surgeons at operation, of which 69 survived; 3 died within six months of carcinoma of islet tissue with metastasis. The neoplasms were usually 1 or 2 cm. in diameter and not infrequently multiple. In one case reported by O'Leary and Womack[3] (Case III), the neoplasm was quite large, measuring 11 by 9 by 9 cm. and weighing 500 Gm.

The following case was thought worthy of recording because of the very large size of this type of tumor (largest yet reported) and because its successful resection again illustrates how radically one may operate upon the pancreas in man.

CASE REPORT

G. P. L. (No. 233821), white, male, aged 32 years, traveling salesman, was admitted to the University of Chicago Clinics Jan. 1, 1940. The present complaints began in April, 1939, when he had a two-hour period of amnesia during which he performed actions automatically. Four days later he experienced an attack of syncope in the street and was revived in a hospital by injections of glucose. Subsequently there were many attacks, characterized by convulsive seizures and periods of stupor. Glucose relieved the attacks and increased food taking diminished their frequency and intensity. In September, 1939, he was hospitalized in another institution where as a result of study a diagnosis of islet-cell, insulin-producing tumor was made and laparotomy was performed. The pancreas was exposed and a tumor mass, measuring about 6 or 7 cm. in diameter, was found at the junction of the body and tail; adjacent to it was a second tumor measuring about 1.5 cm. in diameter. A specimen removed from each mass for frozen section was reported as "adenocarcinoma, Grade III." The abdomen was then closed.

Following operation the attacks continued but by frequent feedings were reduced in severity and frequency, there being a six-week period in which no attacks occurred. These increased feedings resulted in a gain of 25 pounds in weight. During the ten days prior to admission attacks would occur at about 11:00 A.M. but would be aborted by drinking orange juice.

Received for publication, May 20, 1940.

The history was otherwise irrelevant except for the fact that six aunts and uncles on the father's side, the mother and maternal grandmother, and one maternal uncle had died of malignant neoplastic disease.

Physical examination revealed a well-developed obese young adult male weighing 252 pounds, 6 feet in height, mentally alert, and apparently in no discomfort. There were no palpable masses through the thick abdominal wall and no superficial adenopathy. X-rays of the lungs revealed no metastases. An x-ray film of the abdomen showed a large rounded soft tissue mass in the left upper quadrant with small calcium shadows in it. Fasting blood sugar was 48 mg. per cent and following the standard dextrose tolerance test rose to 152 mg. per cent one-half hour after taking dextrose solution, 195 mg. per cent at one hour, 49 mg. per cent at two hours, and 36 mg. per cent at three hours.

I witnessed the onset of an attack at about 11:00 A.M. following breakfast at 8:00 A.M. the morning of admission. The eyes became "glassy," the face flushed, and the patient, with a peculiar staring expression, was unresponsive to questions. Drinking 200 c.c. of a concentrated dextrose solution resulted in a few moments in the return of normal expression and usual keen mental alertness.

It was felt that another laparotomy was indicated to remove the pancreatic tumor if possible, since the general well-being of the patient and the fact that the history of the attacks showed they were not increasing in severity suggested that the neoplasm might not have metastasized. This was performed on Jan. 4, 1940, under nupercaine spinal and ethylene-ether anesthesia. The upper abdomen was entered through an inverted T-incision (Fig. 1). A large mass surrounded by dense adhesions was encountered in the body of the pancreas. Palpation of the liver and exploration of the general peritoneal cavity revealed no gross evidence of metastases. Freeing of the tumor mass was begun by severance of adhesions from the gastrocolic omentum and transection of this. The upper aspect of the tumor mass was adherent to the posterior wall of the stomach. This was freed by cutting away the external muscular coat of the stomach wall over a surface of about 5 by 8 cm. Using the normal size spleen as a handle for the mass, the latter was then brought into the operative wound and finally freed of all adhering tissue except at two points; namely, its junction with the pancreas and over an area about 2 cm. in diameter with the first loop of jejunum. Fearing the latter was a point where tumor cells had infiltrated the wall, the adherent segment was resected. The tumor and spleen were then removed by cutting transversely through normal appearing pancreas (and splenic vessels) about 2 cm. away from the gross limits of the tumor. When the latter step was completed, it was observed that of the pancreas, the head and about 2 cm. of the neck remained. The cut surface of pancreas was sewed over with a continuous suture of fine silk. What was thought to be the main pancreatic duct was ligated separately. Just proximal to the running suture a silk ligature was passed completely around the pancreatic stump and tied snugly. The abdomen was closed in layers with interrupted silk and silver wire tension sutures. A small soft rubber drain was inserted to the large tumor bed.

Subjectively the patient felt quite well during all of the postoperative period. The drain was removed forty-eight hours after operation and in a few days the small amount of serous discharge from the drain tract ceased and the latter closed spontaneously. The night of the operation the temperature rose to 104° F. rectally. A moderate icterus developed on the sixth day but by the fifteenth day had disappeared.

Twenty-four hours after operation the blood sugar was 560 mg. per cent with no acetone or diacetic acid in the urine. One hundred units of insulin were given throughout the first day and the next morning the blood sugar was 299 mg. per

cent. The daily dose of insulin varied from 55 to 70 units for the next eleven days on a 1,200 to 1,500 calorie diet; it was reduced to 20 units a day for the next eleven days, the fasting blood sugars being within normal limits. He was discharged from the hospital Feb. 1, 1940, the fasting blood sugar being 95 mg. per cent without insulin (1,500 calorie diet) the previous day and a normal dextrose tolerance test being obtained. There was no evidence of insufficiency of external pancreatic secretion, the stools being normal except on one occasion when there was a copious, very foul stool. By April 1, 1940, he had resumed his occupation and has remained free from attacks. He was last seen on Dec. 1, 1940, in apparent good health.

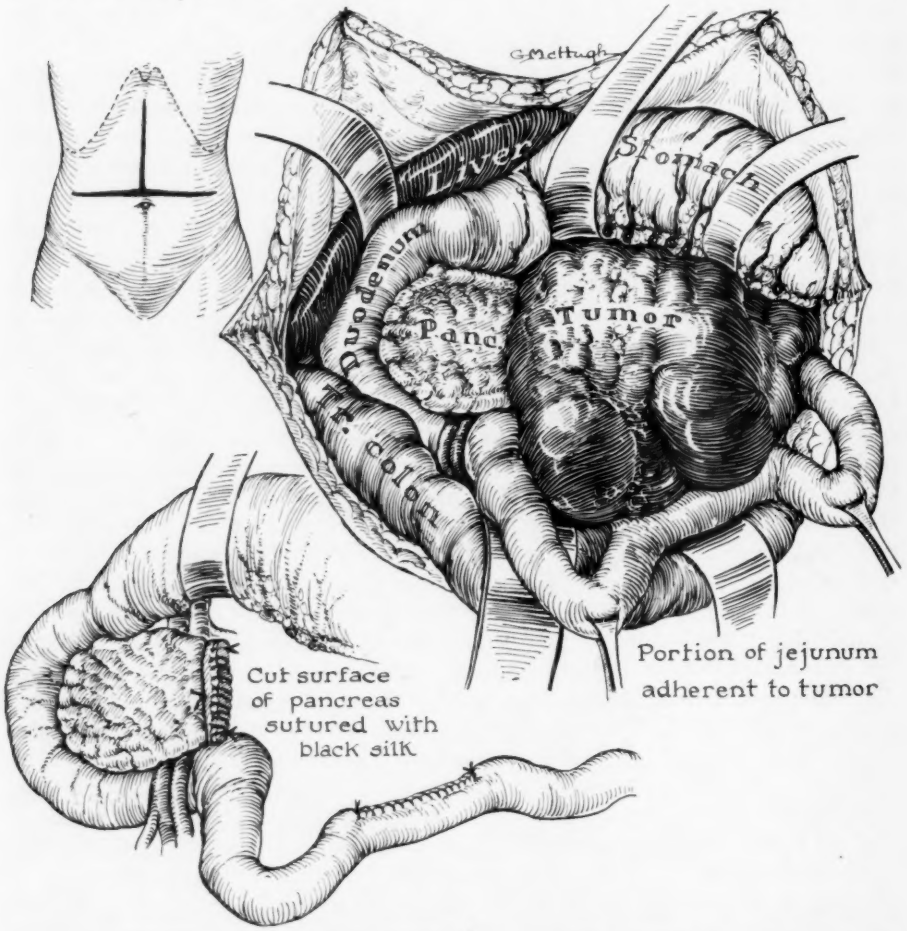

Fig. 1.—Semidiagrammatic representation of operative findings in case reported in the text showing site and relative size of islet-cell tumor, type of incision in the abdominal wall, and treatment of the pancreatic stump after excision of the neoplasm and adherent portion of jejunal wall.

Pathologic Study.—The gross specimen consisted of a spherical nodular tumor mass 15 cm. in greatest diameter by 13 by 10 cm. (Fig. 2). Its capsule appeared intact. Attached at one point was a tongue of normal appeararing pancreas 2 by 1.5 by 1.5 cm. The cut surface of the tumor was fibrotic, yellow streaked, and dull granular in appearance with several calcareous deposits in the center of the mass. It weighed 673 Gm.

Microscopic examination of sections stained by hematoxylin and eosin taken from various portions of the tumor mass showed considerable variation in his-

tologic structure. In the central portion of the mass (Fig. 3*A*) the tissue was very sclerotic, being composed of dense hyalinized anastomosing bands, the interstices of which contained small cords of epithelial cells. There were areas of calcification but no ossification of the hyalinized tissue. Sections taken from elsewhere especially from the more peripheral portions of the tumor (Fig. 3*B*), showed it to be composed of dense sheets of small epithelial cells with varying shape. The cytoplasm appeared for the most part finely granular and the nuclei moderate in size and fairly hyper-

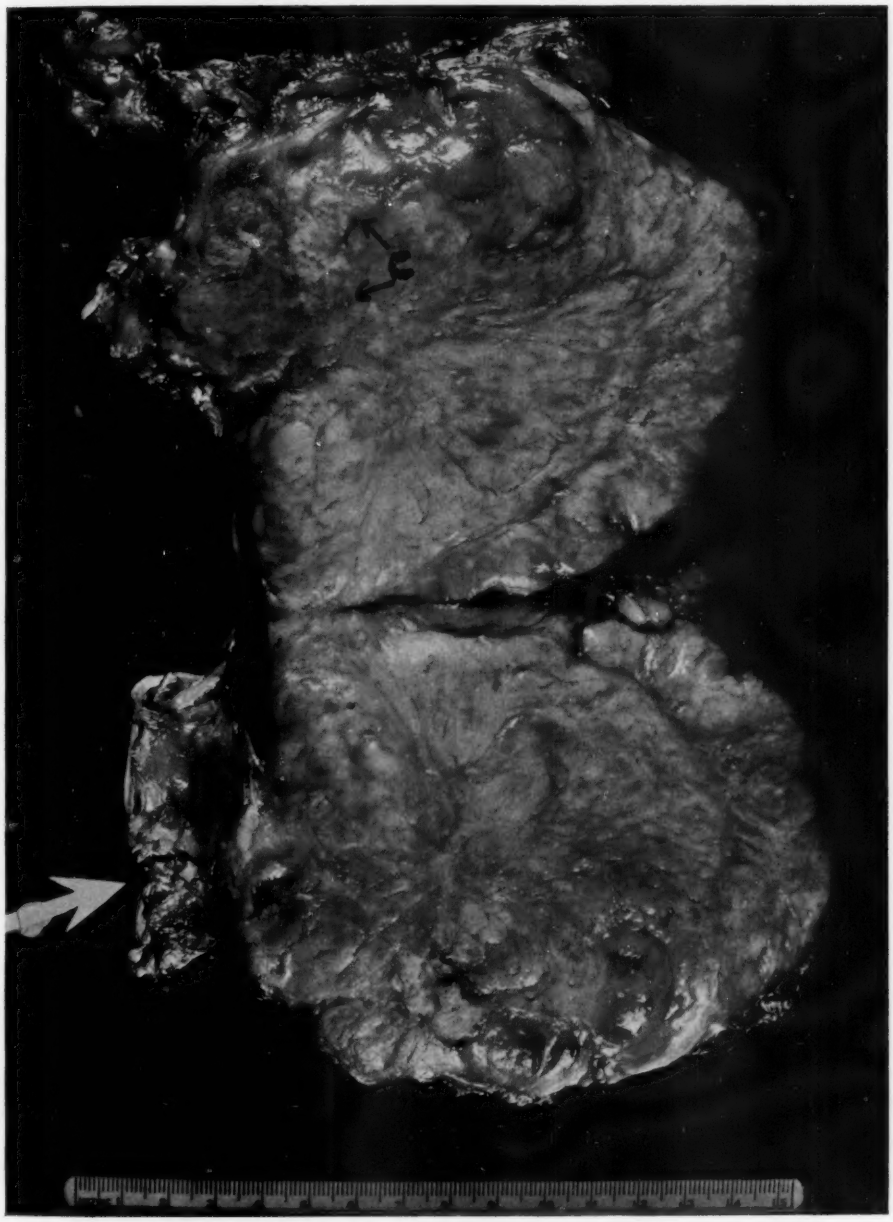

Fig. 2.—Photograph of bisected formalin-fixed islet-cell tumor of the pancreas, showing solid structure throughout. Excised portion of normal pancreas is seen just below the point of the arrow; above this is the segment of outer muscular coat of the posterior wall of the stomach removed with the tumor because of the intimate adherence of the latter. *C*, Calcification in most fibrotic portion of the tumor.

A.

B.

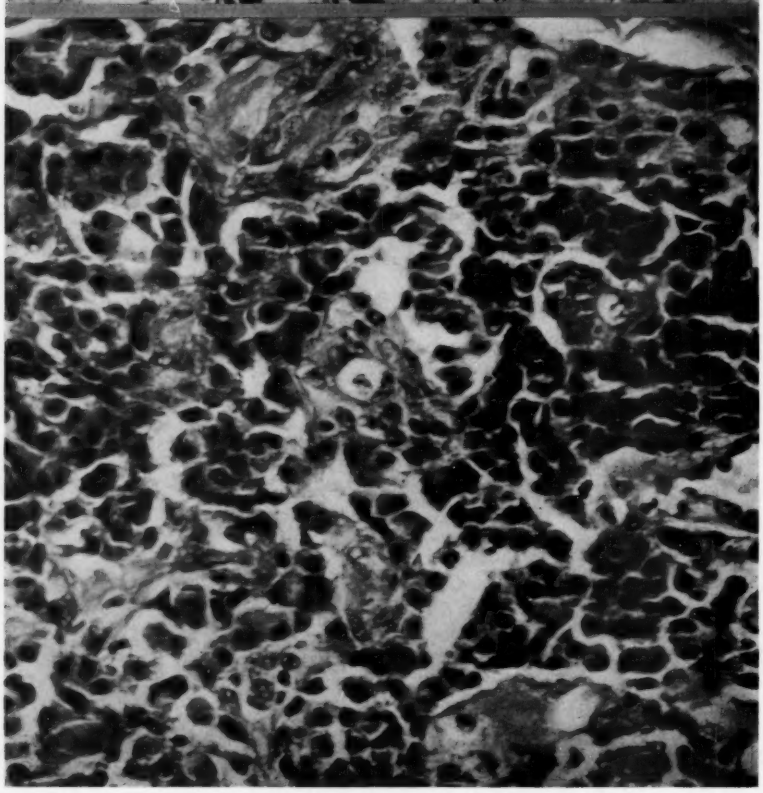

Fig. 3.—*A*, Photomicrograph (×110) of central portion of islet tumor of pancreas, showing dense sclerotic tissue throughout which are scattered irregular cords of tumor cells. A large calcareous deposit is also shown. *B*, Photomicrograph (×450) from area in periphery of tumor, showing dense cellular nature of the tumor in this region. The tumor cells vary in size and shape and suggest a rapidly growing process.

chromatic. In many areas the cells had assumed a rather tall or low columnar appearance and were arranged about small lumina or tended to an acinar organization. Mitotic figures were infrequent. In cross sections of some of the larger veins, masses of tumor cells may be seen within the lumina.

Supravital stains with Janus green and with neutral red were made by Dr. Sylvia Bensley, of the Department of Anatomy. Such stains color selectively the granules of the beta cells. Most of the cells in the sections did not contain granules which stained with these vital dyes, although there were scattered cells which gave a typical beta cell picture. Since, however, the patient had exhibited the typical attacks of hyperinsulinism, it is a justifiable conclusion that in some portions of the tumor there were probably masses of functioning beta cells (neoplastic).

Sections through the segment of excised adherent jejunum showed the presence of typical normal pancreatic tissue, including islets in the jejunal wall extending through to the submucosa. There was a large duct leading from the intramural pancreas into the jejunal lumen. In my opinion this abnormal location of the pancreatic tissue may well represent a grafting of pancreatic tissue from the normal site onto the bowel wall that occurred inadvertently at the previous operation when packs had been placed at the sites of biopsy of the tumor and subsequently, of course, pulled out. The protocol of the first operation made no mention of jejunum being adherent to the tumor or pancreas.

Pathologic Diagnosis: Islet-cell tumor of the pancreas. Taking into consideration the history and gross findings at operation, it is impossible to state whether the neoplasm was benign or malignant.

DISCUSSION

The above case would appear to be of interest because of the unusually large size of the tumor and its rapid growth from about 7 cm. in diameter to 15 cm. in diameter over a period of four months without gross evidence of metastases during this period. This increase in size was not accompanied by a parallel increase in number or severity of attacks as more judicious spacing in the food intake resulted in a fair degree of control of the attacks. This might also indicate a variation in the insulin output of the tumor as a whole due to varying functions in this respect on the part of the tumor cells. From the recorded experience with these tumors it would appear that much smaller neoplasms than the one reported above secreted as large or larger amounts of insulin.

The postoperative diabetes might be accounted for on the basis of relative inactivity of the islets remaining in the normal pancreas tissue due to the large output of insulin from the tumor and by the fact that, when the latter was suddenly withdrawn, the remaining normal pancreas was not prepared to cope with the sudden increased demands upon it. That recovery of adequate function in respect to insulin production did occur is attested to by the fact that after approximately three weeks injections of insulin were not necessary to maintain normal blood sugar levels.

A study of the sections would certainly warrant the diagnosis of malignant neoplasm on morphologic criteria alone. However, from

the biologic standpoint the absence of metastases while the primary tumor grew so rapidly in a relatively young adult would favor the view that the process was, up to operation at least, actually benign, or at least still localized. Previous experience with these tumors has shown that, while they might appear malignant histologically, removal of such growths has resulted in prolonged survival without recurrence of attacks of hyperinsulinism.[4] At the first exploration, two tumor masses were observed. These apparently had fused to form the large tumor found at the second operation. While the smaller tumor might have been a local metastasis, it is equally probable that at the onset there were two distinct neoplasms arising from different islets.

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STRANGULATED HERNIA REDUCED EN MASSE

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THE reduction en masse of a strangulated inguinal or femoral hernia is an extremely rare occurrence. From 1702, when this entity was first described by Saviard, until 1931 Pearse,[1] was able to collect only 190 cases, including 1 of his own. Conner and Hewitt[2] reported 5 cases of reduction en masse occurring in a series of 1,618 cases of strangulated hernia, an incidence of 0.3 per cent. Pearse states that the incidence is approximately 1 in 13,000 cases of inguinal hernia. Since this exhaustive report by Pearse, a total of 15 cases has been added to the literature, as follows: Nason and Mixter, 5 cases;[3] Dunn, 1 case;[4] St. John, 3 cases;[5] White, 1 case;[6] Vail, 1 case;[7] Del Toro, 1 case;[8] Druckerman, 1 case;[9] Abell, 2 cases.[10] The reduction en masse of a femoral hernia is much more unusual than the inguinal type, a total of only 25 cases having been reported to date. We are presenting 2 cases (1 inguinal and 1 femoral) which demonstrate several points of interest.

CASE REPORTS

CASE 1.—W. C. (No. 75032), was admitted to the surgical service of the senior author (M. B.) on Feb. 12, 1939. He gave a history of intermittent, colicky abdominal pain for one hour. About six hours before admission the patient noted a large swelling in the right scrotum which he forcibly reduced. He had noted a mass in this area for the past five years, but it had never been as large as on this occasion. Eighteen years previously the patient had had a right femoral hernioplasty.

On admission the temperature was 98.4° F.; the pulse rate was 60 per minute; and the respirations were 20 per minute. There was moderate lower abdominal tenderness present but no distention. There were no masses palpable, either abdominally or rectally. The right external abdominal ring was enlarged, and a slight impulse was transmitted through the inguinal canal to the examining finger on coughing. The patient developed further signs of intestinal obstruction while under observation, and a scout film of the abdomen revealed fluid levels, indicating intestinal obstruction.

A preoperative diagnosis of intestinal obstruction due to reduction en masse of a strangulated hernia or to a strangulated internal hernia was made, and an operation was performed by Dr. B. N. Berg twelve hours after admission. A right rectus muscle-splitting incision was made. The small intestines were found to be greatly dilated. In the right lower quadrant of the abdominal cavity a mass about 4 inches in diameter was observed. This was extraperitoneal and bulged into the peritoneal cavity. Two limbs of small intestine emerged from this mass, and a constriction was found which had strangulated the bowel. Further exploration determined that the constriction was at the internal abdominal ring. The ring

Received for publication, June 10, 1940.

was divided, and about 6 inches of bowel were withdrawn into the peritoneal cavity. The bowel was viable. A simple purse-string closure of the neck of the sac was performed, and no further attempt was made to repair the hernia. The abdomen was closed in layers. During the closure of the peritoneum it was noted that this structure was extremely relaxed in the right inguinal region. Convalescence was uneventful, and the patient was discharged on the sixteenth postoperative day.

CASE 2.—A. V. (No. 75506), was admitted to the private service of one of us (D. C.) on March 11, 1939. On admission the patient gave a history of severe, colicky abdominal pain associated with vomiting and obstipation for three days. At the onset the vomitus contained old food particles, but it had become fecal in character prior to admission to the hospital. The patient had had a right inguinal hernia repaired fifteen years previously and this had not recurred, but a mass had been noted in the right groin below the old scar on several occasions since the operation. The mass, however, had not been noted for several days preceding the onset of the present illness.

Examination revealed an acutely ill patient evidently in severe distress. The temperature was 98.6° F.; the pulse rate was 86 per minute; and the respirations were 20 per minute. The blood pressure was 128 mm. systolic and 78 mm. diastolic. The abdomen was moderately distended, and tenderness was elicited in both lower quadrants. No rebound tenderness or abdominal rigidity was noted. No masses were palpable either by abdominal or rectal examination. There was a well-healed right inguinal hernia scar with no evidence of recurrence of the hernia. No femoral hernias were noted. The blood examination revealed the following: red blood cells, 6,016,000 per cubic millimeter; hemoglobin, 19 Gm.; white blood cells, 12,900 per cubic millimeter. The differential count showed 71 per cent neutrophiles and 29 per cent lymphocytes. The blood findings indicated a marked hemoconcentration. The urine was normal.

A preoperative diagnosis of acute intestinal obstruction was made, with etiology unknown. Laparotomy was performed three hours after admission through a right rectus muscle-splitting incision. A small amount of serosanguineous fluid was found in the peritoneal cavity. The entire jejunum and upper ileum were markedly dilated, and the bowel wall was thick, edematous, and dark reddish to purple in color. There was a mass about 6 cm. in diameter in the right lower quadrant of the abdominal cavity; it was properitoneal in position and produced a definite bulge into the peritoneal cavity. Two loops of small intestine emerged from an opening in this mass, and a marked constriction of the bowel had occurred at this point. The constricting ring was divided, and about 8 inches of bowel were withdrawn and replaced in the abdominal cavity. Further exploration revealed the sac to be a femoral hernial sac which had been reduced en bloc. The femoral opening appeared to be enlarged while the internal abdominal ring was found to be quite small. The bowel was viable. Because the condition of the patient was very precarious, a simple purse-string suture closure of the neck of the sac was performed without excision and the abdomen was closed in layers. A transfusion of 500 c.c. of citrated blood was given on the operating table. Thirty-six hours postoperatively the patient developed a temperature of 108° F. which persisted for three hours, but this returned to normal in the ensuing twenty-four hours. Otherwise the convalscence was uneventful, and the patient was discharged on the fifteenth postoperative day. Examination three months after the operation revealed the presence of a right femoral hernia.

DISCUSSION

The reduction of a strangulated hernia en masse is, in fact, an apparent reduction whereby the sac or a rim of the sac and the incarcerated

contents are displaced from their accustomed position in the inguinal or femoral canals to an anomalous position which is usually properitoneal. During this reduction the relation of the constricting neck of the sac to the contents is undisturbed, even in those cases in which partial rupture of the sac occurs. An attempt at forceful reduction of a strangulated hernia is the usual cause of this apparent reduction, but frequently it may occur spontaneously and even without the knowledge of the patient (our Case 2; Nason and Mixter, Case 1). In many cases a history of repeated reductions of the hernia by taxis may be elicited, with the last reduction being the most difficult of accomplishment. A considerable proportion of these cases occur in recurrent hernias or in patients who have had a previous operation for an inguinal or femoral hernia.

The exact mechanism of reduction en masse is not thoroughly understood, and several theories have been offered to explain this occurrence. It is generally accepted, as pointed out by Nason and Mixter, that certain conditions must obtain before reduction en masse can occur: (1) the neck of the sac must be sufficiently small to retain and incarcerate the contents, (2) the sac must be freely movable in the inguinal or femoral canals and not attached firmly to any of the structures in these canals, and (3) the neck of the sac must be sufficiently mobile and detached from the internal ring (in inguinal hernias). Unless these conditions are present, a reduction en masse cannot take place and the strangulated hernia either will be reduced completely and satisfactorily or will remain as an irreducible strangulation.

One theory advanced to explain the mechanism of false reduction is that the presence of a large preformed properitoneal space, such as might be due to excessive properitoneal fat, is a predisposing cause. In Case 1 of our series the surgeon noticed an extremely lax peritoneum which would account for the presence of a large properitoneal space. Pearse[1] suggests that in many cases a combined or bilocular sac is present, consisting of an inguinal pouch and a properitoneal pouch. In these cases the strangulated bowel can be displaced from the inguinal to the properitoneal pouch. He states that in 15.5 per cent of the recorded cases such an inguinal properitoneal sac was present with the strangulated intestine in the properitoneal portion. He also states that in 77.3 per cent of the cases the entire sac and contents were displaced to a properitoneal position.

It is our belief that the reduction of a strangulated inguinal hernia en masse depends on the relationship between the internal abdominal ring and the neck of the sac. Ordinarily, attempts at reduction of a strangulated inguinal hernia will result in (1) complete and satisfactory reduction, (2) no reduction and persistence of the external position of the strangulated hernia, or (3) reduction en masse. The result will

depend in large measure on the resistance offered to reduction by the transversalis fascia at the internal ring and the constricting neck of the sac. If neither of these constrictions is exceptionally tight, a complete and satisfactory reduction will occur. If both remain firm, attempts at reduction will fail and the strangulation will persist. If, however, the constriction of the neck of the sac is unyielding, while the internal ring is lax, a reduction en masse will occur, providing, of course, that the three conditions enumerated above as prerequisite for this occurrence are present. When a hernia has been present for some time and has been reduced frequently, it is not unusual to find a relaxed internal ring with separation of the transversalis fascia from the layers of the sac. In fact, the transversalis fascia may be extremely attenuated at this point. When strangulation supervenes in a case of this kind, it is probably caused by fibrosis and stricture of the neck of the sac alone and bears no relation to the relaxed internal ring; a situation is set up wherein reduction en masse can occur. When the strangulation occurs at the external abdominal ring, the above circumstances undoubtedly do not prevail because of the firmness of the arched fibers of the external oblique aponeurosis forming this ring. It is probable that with this type of strangulation reduction en masse rarely occurs because the primary constricting factor is the aponeurotic structure and not the neck of the sac. Inasmuch as a great percentage of strangulations occur at the external ring, this may explain the rare occurrence of reduction of a strangulated hernia en masse.

DIAGNOSIS

The history and symptomatology in a typical case afford the surest means of establishing a correct diagnosis. Usually the hernia has been present for many years and has been successfully reduced many times during this period. Frequently a history of an operation for an inguinal or femoral hernia may be obtained. As a rule, the last reduction was accomplished only after excessive manipulation and probably was accompanied by pain; finally, the expected relief of the symptoms of strangulation did not occur. This is the usual story and, when obtained in conjunction with symptoms of vomiting, colicky abdominal pain, and obstipation, the diagnosis readily follows. In many cases, however, the typical sequence of events does not occur. The patient may have been completely unaware of the presence of a hernia, and consequently no history of taxis is obtained. In other cases the hernia is reduced with great ease or reduces itself spontaneously. In cases of this type the inguinal or femoral rings are undoubtedly relaxed, and the strangulation is due to fibrosis and stenosis of the neck of the sac. Another finding which occasionally obscures the diagnosis is the period of temporary respite from symptoms immediately following the reduction en masse. This period may last from a few hours to several weeks and is sufficient

in many instances to obliterate from the patient's mind the memory of the reduction of the hernia. As a result the symptoms of intestinal obstruction, when they do occur, are not associated with a strangulated inguinal or femoral hernia, and the correct diagnosis is not made.

The common sequence of events may then be briefly summarized as follows:

1. An inguinal or femoral hernia has been present for several years and may have been operated upon previously.
2. This hernia has become incarcerated several times but has always been reduced by manipulation.
3. The last reduction was accomplished with more difficulty and was accompanied by pain.
4. The symptoms of intestinal obstruction do not subside as expected or subside for only a brief interval.

Physical examination, except for establishing the fact that intestinal obstruction is present, rarely aids in establishing the etiological factor in cases of reduction en masse. Moderate abdominal distention is usually present, and tenderness over the lower quadrants of the abdomen may be elicited. A mass may be palpated occasionally by abdominal or rectal examination, but this is a relatively uncommon finding. The palpation of an abdominal mass with the examining finger in the inguinal canal is very significant, especially when a pertinent history has been obtained. Very frequently the external abdominal ring is enlarged. Nason and Mixter point out that a definite defect is commonly noted in the inguinal canal with only a very feeble impulse transmitted to the examining finger on coughing.

TREATMENT

The treatment of reduction en masse of a strangulated hernia is surgical. With intestinal obstruction of the strangulating type, treatment by suction with either the Wangensteen or the Miller-Abbott tube is definitely contraindicated. After preliminary treatment to restore the fluid and electrolyte balance, immediate laparotomy should be undertaken. We feel that in all cases the incision of choice is a muscle-splitting rectus incision. When doubt as to the diagnosis is present, this incision will probably be employed, but it is indicated likewise in those cases in which the diagnosis has been definitely established. Proper exploration and resection of the bowel, if necessary, are much more easily accomplished through this incision than through an oblique inguinal incision, and, if it is deemed advisable, a repair of the hernia may be carried out from within the abdomen. We believe that relief of the strangulating obstruction is the primary aim of therapy and that little time should be spent on repair of the hernia, particularly since many of these patients are in poor condition from an obstruction of several

days' duration. The strangulated bowel should be carefully examined because of the possibility of minute rupture of the bowel wall having occurred as a result of overenthusiastic attempts at reduction.

The postoperative treatment is that of any strangulated hernia. In this period Wangensteen suction may be employed to great advantage to prevent distention of a possibly damaged bowel. Parenteral fluids and transfusions are employed when indicated.

The mortality rate depends almost entirely on the length of time elapsing between the onset of obstruction and the operative relief of the obstructing mechanism. Pearse states that in a collected series of 164 cases of the inguinal type the mortality was 40 per cent, while in twenty-four cases of femoral hernia the mortality was 70 per cent. With early diagnosis and operation through a rectus or midline incision the mortality rate should be no higher than for strangulated hernias not complicated by reduction en masse.

SUMMARY AND CONCLUSIONS

1. Two cases of reduction en masse of a strangulated hernia are reported, making a total of 207 cases in the literature.

2. The mechanism of reduction en masse is discussed. A theory is presented which explains this occurrence on the basis of changing relationships between the internal abdominal ring and the neck of the sac.

3. The diagnosis is usually made on the basis of a history of reduction of an incarcerated hernia without subsidence of the symptoms of obstruction.

4. Treatment is always surgical. It is important that the abdomen be opened through a muscle-splitting rectus incision.

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ACUTE COMPLETE OBSTRUCTION OF THE HEPATIC VEINS

Report of Case Simulating an Acute Abdomen

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OBSTRUCTION to the hepatic veins is a relatively uncommon condition, but perhaps it is not as unusual as we have been inclined to believe. In 1845 George Budd, Professor of Medicine at King's College, reported a case of a man who died in the King's College Hospital from idiopathic thrombosis of the hepatic veins. In 1899 Chiari, of Prague, described three similar cases of his own and reviewed the literature. Accordingly, on the Continent the condition is known as Budd's or Chiari's disease. In 1920 Hoover[1] reported some thirty cases from the literature since which time there have been quite a number of isolated cases reported.

A variety of causes may operate to result in obstruction to the hepatic veins. Pressure from without by tumors, gummas, enlarged glands, etc., may be found. Congenital malformations, particularly of the vascular bed, may be factors. Actual disease of the veins themselves, either inflammatory or neoplastic or cicatricial, may exist. A primary endophlebitis has been reported occasionally. Most frequently, however, the process is part of a more general one, involving the inferior vena cava and/or the portal vein with its tributaries. The condition also may be due to a septic embolus which has lodged somewhere in the vessel and resulted in thrombus formation.

Various chemical poisons may cause the condition. It is also seen with polycythemia vera, although cerebral or peripheral vessels are more commonly involved than intra-abdominal ones.

In discussing hepatic complications of polycythemia vera, Sohval[2] says: "Patients with polycythemia vera commonly consult a physician because of vascular thrombosis." He remarks upon the rarity of thrombosis of the hepatic veins in polycythemia vera but reports such a case with dyspnea, weakness, ascites, enlarged liver, jaundice, and fever. Occasionally, this condition is seen following splenectomy during the critical postoperative phase in which the thrombocytes arise to a very high level.

Apparently obstruction to the hepatic veins occurs more commonly in young people. Savin[4] gives the average age as 28.5 years. Sex seems to have no influence, for males and females show about the same incidence. The large majority of patients give no history of any definite symptoms previous to the onset of the obstruction.

Received for publication, June 24, 1940.

Obviously a complete obstruction of the hepatic veins results fatally in a short time, and during this period there is marked passive congestion of the liver and spleen; in addition there are the findings associated with portal obstruction, such as edema of the wall of the intestine drained by the portal vein, ascites, etc. An incomplete or partial obstruction may cause complete fibrosis of the lobe or lobule of the liver involved, with symptoms similar to those found in complete obstruction but less severe.

Symptoms of this condition will depend upon the extent of the process. A mild degree of obstruction may cause no symptoms at all. A gradual or chronic type of obstruction will give rise to symptoms very similar to those occurring with portal cirrhosis. There will be epigastric distress, some enlargement of the liver and spleen, ascites, dilatation of collateral veins, etc.

The acute type, which seems to be the more frequent type encountered, comes on suddenly and may simulate closely some acute surgical lesion of the abdomen. The onset is usually abrupt with severe abdominal pain located in the upper abdomen; often there is persistent nausea and vomiting; there may be a slight icterus; elevation of the temperature may occur, but more frequently the temperature is subnormal; the pulse becomes rapid and the patient appears to have suffered a major abdominal catastrophe. Examination discloses an enlarged liver, the margin of which is tender but smooth; splenic enlargement may be made out if spasticity of the abdominal muscles permits; the abdomen is distended and hard; free fluid is usually present within the peritoneal cavity in varying amounts. The patient is bathed in perspiration and has a marked pallor. Occasionally, there may be a cyanosis of a lilac shade. The white blood count is usually markedly elevated with a preponderance of neutrophiles. The urine may show evidence of renal irritation and perhaps a trace of bile. Commonly these patients with an acute obstruction become rapidly worse and die within thirty-six to forty-eight hours after the onset. It is easy to understand how a case presenting such symptoms may be considered a surgical problem and may be subjected to exploration. The literature does not record many such errors, but I believe this is due either to failure of recognition or to lack of interest. In discussing portal thrombosis, a closely associated condition, Pallette[3] describes a case in which the diagnosis of ruptured ectopic pregnancy led to exploration of the abdomen.

The diagnosis of obstruction of the hepatic veins is usually made post mortem, although there are a few confirmed reports of ante-mortem clinical diagnoses.

Case Report.—D. M., a male, aged 26 years, entered the hospital on April 23, 1940, with the complaint of severe upper abdominal pain of forty-eight hours' duration and vomiting for twenty-four hours. The pain was described as cramplike and was located just below the xiphoid.

The patient's past history was essentially negative, although he had been "slowing up" for several months and had had a little indigestion. There had been no recent colds or dyspnea nor other possible exciting factors.

The present illness had commenced forty-eight hours previously with a crampy pain in the upper abdomen; later it became steady and generalized. Vomiting began twenty-four hours before admission and had been continuous. There had been some diarrhea for forty-eight hours, frequent watery stools without tenesmus.

The patient looked sick upon admission. His face was flushed, but he had a pinched expression. He was clear mentally and responded promptly to questions. The tongue was dry and coated. The sclera had an icteroid tinge. The heart and lungs appeared negative. The temperature was 103.6°; pulse, 140; respirations, 28; blood pressure, 118/76. The abdomen was distended throughout. There was marked tenderness in the upper half and rigidity of the entire abdomen. There was tympany in the midabdomen with dullness in both flanks. The liver dullness was noted not to be diminished and in fact was thought to be increased. Free fluid was detected in the flanks. Rectal examination was negative. The white blood count was 16,160. The urine showed a trace of albumin and a few red blood cells. No x-rays were made. Blood chemistry studies reported later showed a blood sugar of 33 mg.; N.P.N., 98 mg.; urea N, 41 mg. per 100 c.c. of blood. The blood Wassermann was reported negative. The clinical impression was that we were dealing with an acute abdomen, probably a perforated peptic ulcer.

The patient was prepared for operation and given 1,000 c.c. of 10 per cent dextrose intravenously.

An upper right rectus incision was made and enlarged later for exploration. As soon as the peritoneum was opened, there was a leakage of clear, bile-tinged fluid of which some 50 ounces were removed by suction. No perforation was found and no evidence of acute exudate noted. The liver and spleen were markedly enlarged, blue-black in color, smooth, and very hard. The mesentery and intestinal wall were edematous throughout; there were very many petechial hemorrhages in the serosa of both; the mesenteric glands were enlarged and the portal vein distended. Convinced that the condition was one of portal thrombosis, a biopsy of the liver was made and then the incision was closed.

Following operation, the patient became weaker, continued to vomit, and expired about twelve hours later.

A post-mortem examination showed the following interesting findings: There was about 2,500 c.c. of clear, straw-colored exudate in the peritoneal cavity. The diaphragm was pushed up to the level of the third interspace on the right and the fourth rib on the left. The mesenteric nodes were generally enlarged. The mesentery was edematous and its vessels congested. The pleural cavities contained about 300 c.c. of a fluid similar to that in the peritoneal cavity. The pericardial fluid was increased in amount and bile tinged. The right heart was dilated. The endocardium of the left ventricle showed petechial hemorrhages. The lungs were not remarkable. The spleen was greatly enlarged and mushroomed up against the diaphragm. The stomach and intestine showed some congestion but otherwise were negative. The liver was enlarged and weighed 2,300 Gm. Its surface was dark red and firm. Sections showed the liver markings to be obliterated and numerous pale areas were noted which had a yellow-green color. The large vessels throughout the liver were dilated. Their walls were thin and they contained blood clots within the lumina. The portal vein and its tributaries, the splenic and mesenteric veins, were dilated and filled with coagulated blood which was loosely attached.

Microscopic examination of the removed organs revealed interesting changes. The heart showed marked fragmentation of the muscle fibers; the fibers were swollen and edematous. Scattered throughout were numerous leucocytes, of which many were polymorphonuclears. Numerous sections of the liver were studied and these

all showed widespread hemorrhage and necrosis. Small islets of relatively normal appearing liver parenchyma appeared about the portal triads. The central veins and the adjacent sinusoids were markedly engorged. The liver cells of the central part of the lobules were indistinct and leucocytic infiltration was evident. The portal veins were greatly distended with blood, but definite thrombosis of the smaller radicles was not observed. Some of the sections included large veins located near the periphery of the liver or outside of it. These veins all exhibited varying degrees of thrombophlebitis. One vein showed an organizing thrombus invaded by fibroblasts and attempts at canalization. Other large veins showed a fibrinous exudate adherent to the endothelium. In another section a large vein was seen partly filled by a thrombus showing fibroplastic organization.

DISCUSSION

The predominating pathology in this particular case would seem to be in the liver and takes the form of acute passive congestion of extreme degree with widespread hemorrhage and necrosis of the liver parenchyma. Such findings strongly suggest a sudden and complete blocking of the portal circulation proximal to the central veins of the liver. Sections show thrombophlebitis and complete thrombosis with beginning organization of the large veins of the liver. Grossly, the primary thrombosis was thought to be in the portal veins, but the existing changes in the liver can be more readily explained on a basis of obstruction of the hepatic veins.

The etiology of the thrombosis cannot be definitely determined. The acute onset in a person thought to have been previously well would seem to eliminate many of the possible etiological factors which are mentioned above. The post-mortem material fails to reveal any noteworthy evidence of such factors. The findings of acute myocarditis, cloudy swelling of the kidneys, and mesenteric lymphadenitis certainly suggest that infection did play an important role. Finally, we know that in certain instances no definite factor can be made out and such cases are described as idiopathic progressive thrombosis, of which this case may be an example.

CONCLUSIONS

A case of acute, complete thrombosis of the hepatic veins due to infection or idiopathic in origin is recorded with the principal post-mortem findings.

The patient had been subjected to exploratory laparotomy under the impression that the condition was an acute surgical emergency.

The literature of this condition is briefly reviewed.

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SYPHILIS OF THE STOMACH NECESSITATING TOTAL GASTRECTOMY*

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SYPHILIS of the stomach necessitating total gastrectomy is rare. Poole and Foster[1] reported the first case in 1931, and a thorough search of the literature fails to reveal any other similar case. It is interesting to note that total gastrectomy, an uncommon procedure and associated with a mortality rate of 40 to 50 per cent,[2] was successful in the case of Poole and Foster and in the one reported here.

CASE REPORT

History.—R. S., a negro man, aged 31 years, was admitted to the medical service of the John Gaston Hospital on July 21, 1939, complaining of inability to "keep food down" of four months' duration. Vomiting at the onset of his present illness occurred at infrequent intervals, and the vomitus contained undigested food particles. The intervals between vomiting gradually shortened until the time of admission to the hospital, when all solid food was vomited soon after its ingestion. At no time in the course of his illness had the patient had pain. The most discomfort that he had ever felt was a sense of "fullness" which occurred just before, and was relieved by, vomiting. The patient stated that he had never vomited any blood nor had his stools been black.

Prior to the onset of the present illness he had never had any digestive disturbances of any description.

In 1933 the patient received "ten shots" for his blood, but the history of primary or secondary syphilitic lesions could not be obtained.

There was no evidence of syphilis obtained from the family history.

Examination.—Physical examination revealed a young negro adult showing a marked degree of malnutrition and dehydration. No further facts could be elicited by physical examination. The abdomen presented no palpable masses and no areas of tenderness.

The red blood cell count was 4,130,000 per cubic millimeter. The value for hemoglobin was 12 Gm. The white cell count was 7,950 per cubic millimeter, with lymphocytes, 25 per cent; neutrophiles, 73 per cent; and eosinophiles, 2 per cent. The Wassermann and Kahn reactions were positive.

Gastric analysis showed a complete absence of free hydrochloric acid and a total acid of three degrees.

Roentgen Examination (Dr. W. E. D. Anderson†).—After the oral administration of barium sulfate roentgen examination showed a moderately dilated esophagus. The barium mixture entered the stomach readily, but, except for a faint trace, did not pass beyond the cardia. There was a funnel-shaped projection of barium,

*The illustrations for this paper were prepared by Dr. J. L. Scianni, medical illustrator for the Department of Pathology, the College of Medicine, University of Tennessee.

Received for publication, June 26, 1940.

†From the Department of Radiology, the College of Medicine, University of Tennessee.

smooth in outline, which extended into the body of the stomach for about 2.5 cm. The main portion of the body was markedly constricted. The funnel-shaped outline of barium was remarkably smooth. After further ingestion of barium sulfate it was noted that the cardiac orifice remained open and a considerable amount of the mixture was regurgitated into the widened esophagus (Fig. 1). Only a very small amount of barium trickled through the strictured area of the stomach. After six hours there was about 90 per cent retention of barium above the stricture.

Dr. Anderson concluded from his roentgen examination that the gastric lesion was benign.

In consultation with the Medical Service I advised surgical relief of the obstruction, but the patient declined the operation and signed his release from the hospital on July 27, 1939.

On Aug. 30, 1939, the patient returned to the hospital and was admitted to the Surgical Service. The amount of food tolerated was considerably less than it had been one month previously. Only fluid in small quantities was retained. His weight was 116 pounds, which was 70 pounds below normal. Dehydration was marked.

The patient was prepared for surgery by the parenteral administration of dextrose, physiologic saline solution, and vitamin concentrates.

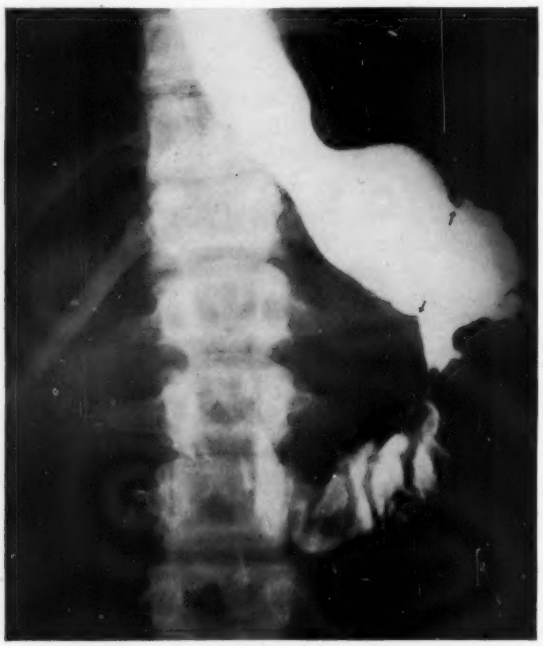

Fig. 1.—Roentgenogram shows almost complete obstruction at the juncture of the fundus and body of the stomach. The arrows mark the esophagogastric union. Note the lengthening and dilatation of the abdominal esophagus which was interpreted as gastric fundus before operation.

Operation.—On Sept. 6, 1939, under intratracheal cyclopropane anesthesia the abdomen was opened through a long, left rectus incision. The liver was about three-fourths normal size, and the reduction in size was particularly marked in the left lobe, the lateral border of which just overlapped the medial border of the esophagus. The liver was a light gray, and its surfaces presented small scars. There were numerous thin adhesions between the liver and diaphragm. The spleen was about three times normal size, and its upper posterior surface was densely adherent to the anterior surface of the body of the stomach. The stomach was

two-thirds normal size, its surface wrinkled. The curvatures of the stomach were almost obliterated by an infiltrating process which left the stomach a straight, thick, and leathery tube. The infiltration began about 2.5 cm. proximal to the pylorus and extended upward to the esophagus. The walls of the stomach were thick, and at the juncture of the body and cardia a complete stricture could be palpated. The esophagus was elongated and extended about 5 cm. below the diaphragm. Its transverse diameter was approximately twice normal (Fig. 2).

The adhesions between the left lobe of the liver and diaphragm were severed, and the left lobe was retracted; this allowed adequate exposure without severing the coronary ligament. The two curvatures were next freed, after dissecting the spleen from its attachment to the stomach, and the duodenum was cut across just distal to the pylorus (Fig. 3*A*). The distal end of the duodenum was closed, and the suture line buried in the peritoneum over the pancreas. The jejunum was then brought anterior to the transverse colon, and a point about 18 inches below the ligament of Treitz was selected for anastomosis to the esophagus. The stomach was used for traction while two posterior rows of sutures were taken between the esophagus and jejunum (Fig. 3 *B* and *C*). After the esophagus and jejunum were thus securely attached, the stomach was removed with about 5 mm. of esophagus and the end-to-side anastomosis completed. Enteroenterostomy was not done (Fig. 3*D*). The abdominal wall was closed with through-and-through sutures of silk. The patient was given a 500 c.c. blood transfusion and returned to the ward in fair condition.

Fig. 2.—Drawing of the pathology in situ. The liver is smaller than normal; its surface is scarred; and adhesions fix its superior surface to the diaphragm. The adhesions to the left lobe have been severed, and the upper end of the stomach exposed. Note the thick, wrinkled, and straightened stomach with the enlarged spleen adherent to it.

Pathologic Report (Dr. W. A. D. Anderson) *Macroscopic.*—The specimen was a thick-walled tubular stomach measuring 14 cm. in length and 6 cm. in circumference (Fig. 4). At its thickest part the wall measured 8 mm. At the upper end of the specimen esophageal mucosa was evident and was white in color and relatively smooth. The esophageal mucosa merged, in an indefinite line, into the mucosa of the stomach. The gastric mucosa at this point was of a dark gray

color, rough, and granular but without definite rugae. An irregular area of ulceration was present in the proximal portion about 4 mm. beyond the distal margin of the esophageal mucosa. This ulcer measured 13 mm. in its maximum diameter. It had sharp punched-out walls, and the edges, particularly at its distal margin, were undermined. It extended to a depth of 5 mm., and the wall of the stomach forming the base of the ulcer was 3 mm. thick. The base was irregular, rough, and of a dirty gray color, and it was covered by opaque, necrotic material. The remainder of the gastric mucosa presented many tiny areas of superficial ulceration and pin-point hemorrhages. The gastric wall gradually thinned out in the distal third to a 2 mm. thickness. The distal ⅔ cm. of the specimen was part of the duodenum. In this portion the mucosa was intact, light yellowish white in color, and markedly rugose.

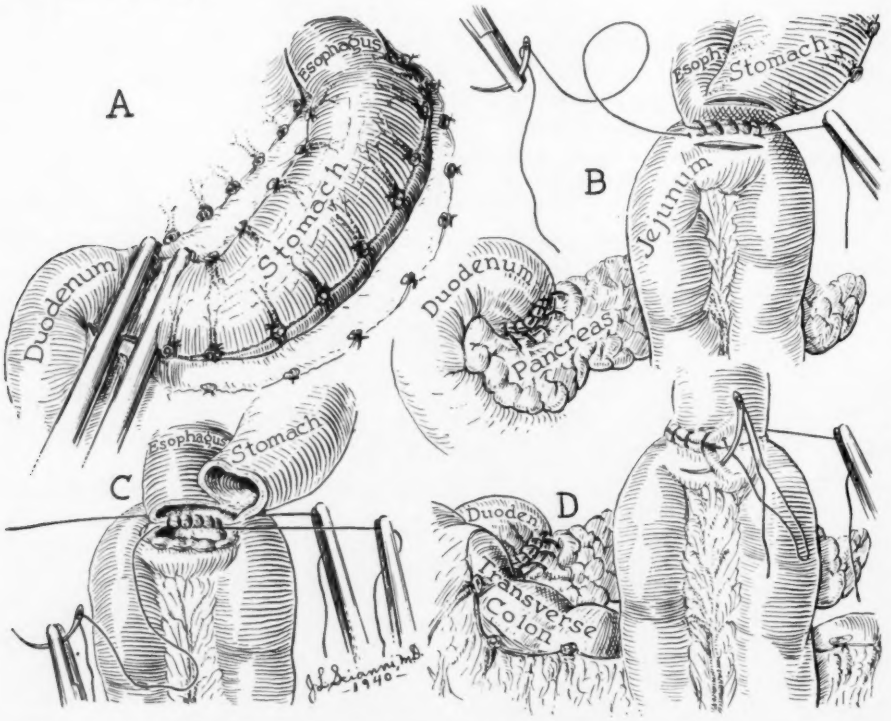

Fig. 3.—*A*, The greater and lesser curvatures have been freed, and clamps have been placed on the duodenum just distal to the pylorus. *B*, The duodenal stump has been closed, and the suture line has been reinforced with posterior peritoneum over the pancreas. The stomach has been turned upward and used for traction while the posterior approximation of the esophagus and the jejunum is made with a continuous catgut suture through the serous and muscular layers. The jejunum has been brought anterior to the transverse colon, and a point approximately 18 inches from the ligament of Treitz has been selected for anastomosis. *C*, The esophagus and jejunum have been opened and cleaned by suction, and the internal row of continuous catgut suture begun. Note that, not until the posterior internal row of sutures is finally placed, is the stomach completely severed at its proximal end. This is a most important step because, when the stomach is used for traction until the esophagus and jejunum are securely united by the two posterior rows of sutures, the most difficult technical handicaps are overcome. *D*, Here the stomach has been completely removed; the internal row of sutures has been completed anteriorly with a Connell suture; and the posterior approximating suture has been brought around and is being used as a continuous suture anteriorly to complete the anastomosis. A jejunojejunostomy is not done.

At the proximal end of the specimen the esophagus was dilated to a circumference of 6.5 cm. In the stomach the lumen was greatly narrowed and in the central portion measured only 1.5 cm.

The thick wall of the stomach was very firm and fibrous. The muscular layers could not be grossly identified.

Fig. 4.—Photograph of the fixed gross specimen. At the upper end a distinct rim of esophagus may be easily recognized, and a comparison of its dilated lumen may be made with narrowed lumen of the stomach. The walls of the stomach are thick with light fibrous tissue. At the lower end of the specimen normal duodenal mucosa is seen.

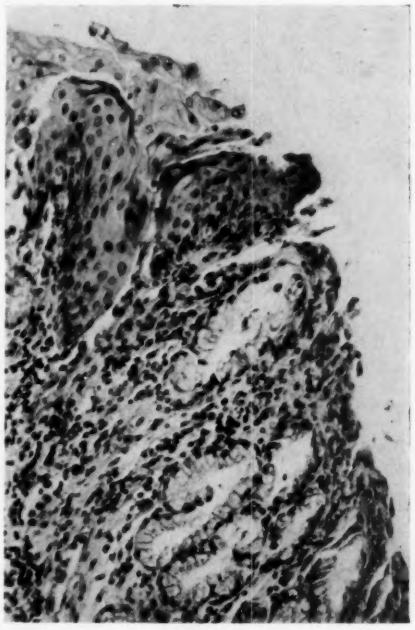

Fig. 5.

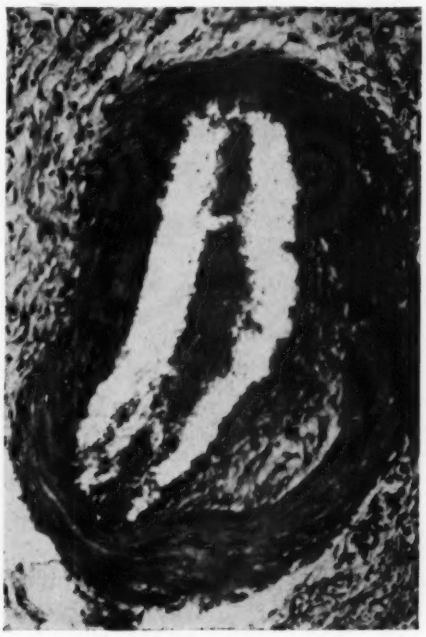

Fig. 6.

Fig. 5.—Microscopic section taken so as to include part of the esophageal wall and part of the gastric wall. The stratified squamous epithelium of the esophagus is seen as it joins with the gastric mucosa. Round cell infiltration may be seen extending to this level in the stomach.

Fig. 6.—Photomicrograph showing intimal thickening and obliterative arteritis.

Microscopic.—A section taken through the gastroesophageal juncture (Fig. 5) showed the squamous epithelium of the esophagus as it merged with the gastric mucosa. The wall in this portion of the stomach was greatly thickened by fibrous connective tissue which was most prominent as a layer between the circular and longitudinal layers of muscular tissue. This fibrous layer ended abruptly at the margin of the esophagus. There was an irregular, diffuse infiltration by round cells which was most prominent around or near small arteries. The same small blood vessels showed a rather marked degree of endarterial fibrous thickening (Fig. 6).

A section taken from the stomach wall showed a superficial area of ulceration of the mucosa with a dense exudate of fibrin and polymorphonuclear leucocytes on the surface. Beneath this in the submucosa there was a dense collection of chronic inflammatory cells, mainly plasma cells and lymphocytes but with some eosinophiles and polymorphonuclear cells. Some granulation tissue was present here at the base of the ulcer. Deeper in the submucosa the collections of chronic inflammatory cells were most prominent around or near small blood vessels. Some mild chronic inflammatory infiltration extended between muscle bundles in the muscular coat. There was some increase of connective tissue in the subserosa.

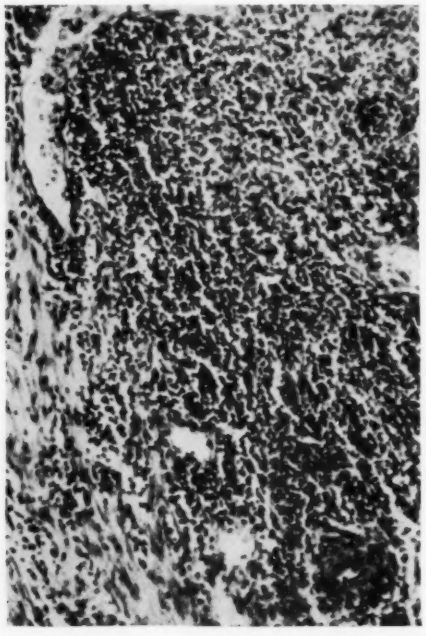

Fig. 7.

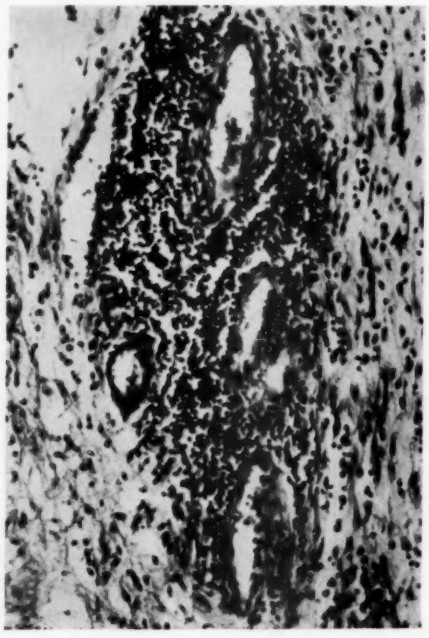

Fig. 8.

Fig. 7.—Another photomicrograph showing focal infiltration which some authors designate as miliary gummas. The cells are lymphocytes with an occasional plasma cell and eosinophile.

Fig. 8.—Rather marked perivascular infiltration with lymphocytes, plasma cells, and an occasional eosinophile.

In a section from a different portion of the wall formation of connective tissue was more marked. Focal (Fig. 7) and perivascular (Fig. 8) collections of lymphocytes were prominent, and intimal thickening of small arteries was present. Superficial small hemorrhages were present.

Several sections of tissue were studied by the Levaditi technique. There were occasional strands of tissue which took the silver stain, but these were so infrequent and so indefinite in detail that their identification as spirochetes seemed unjustifiable.

Postoperative Course.—Convalescence was remarkably smooth and uneventful. Continuous suction siphonage of the jejunum was maintained for seventy-two hours, at which time the indwelling catheter was removed and small amounts of water were allowed by mouth at frequent intervals. There was a gradual increase in quality and quantity of food until the fourteenth postoperative day. At that time the patient was on a complete diet with the vegetables puréed and the meat ground and taking five small meals per day. (It is interesting that from the third postoperative day the patient complained of a ravishing hunger.)

The patient's gain in strength and weight was steady. He was discharged on Oct. 6, 1939, to the Out-Patient Department to receive antisyphilitic therapy. He has been very uncooperative, refusing all medical treatment and ignoring dietary instructions. He was last seen March 10, 1940, six months after operation, when his weight was 157 pounds, 41 pounds above the preoperative weight. He was eating a full diet, and his only precaution was the "chopping-up" of his food. Soon after he left the hospital, too rapid eating of food was followed by regurgitation, but at the present time the patient states that he can eat as much as anyone else and that he eats more often only because he is hungry all of the time.

His red blood cell count six months after operation was 3,750,000 per cubic millimeter with a hemoglobin value of 12.5 Gm. His red cell count has been consistently between 3,500,000 and 4,000,000 since operation.

TABLE I

CLINICAL FINDINGS	POOLE & FOSTER (1 CASE)	AUTHOR'S CASE
Age (years)	37	31
Sex	F	M
Race	W	C
Symptoms of gastric obstruction	Yes	Yes
Progressive weakness & wt. loss	Yes	Yes
Hematemesis	No	No
Duration of symptoms	12 mo.	4 mo.
Gastric HCl (fasting)	Free, 0; total, 4	Free, 0; total, 3
Wassermann reaction	Positive	Positive
Total R. B. C.	5,000,000	4,130,000
Hemoglobin	100%	12 Gm.
Palpable mass	No	No
Diffuse involvement of stomach	Yes	Yes
Total gastrectomy necessary	Yes	Yes
Recovery	Yes	Yes
Developed pernicious anemia	Yes	Too early

COMMENT

Table I shows the remarkable similarity between Poole and Foster's case and mine. Eusterman[3] has described very accurately the clinical picture of syphilis of the stomach which these two cases typify. After reviewing the literature and reporting ninety-three additional cases from the Mayo Clinic, he stated that the clinical characteristics of syphilis of the stomach are ". . . the comparative youth of the patient (average age 34), the short duration of the symptoms in comparison to those of duodenal ulcer and the fact that they are more comparable to carcinoma than to ulcer, the high incidence of positive Wassermann reactions, the almost invariable absence of free hydrochloric acid in the gastric content, and its low concentration when present, and the characteristic filling defect, usually prepyloric and often accompanied by

dilatation of the duodenal cap. . . .'' He also emphasized that there is less emaciation, anemia, bleeding, and pain than one usually finds with other lesions producing such deformity as seen on the roentgenologic examination.

It is further noteworthy that the pathologic picture in Poole and Foster's[1] case and the one reported here, although not conclusive when considered alone, is consistent with a diagnosis of syphilis and serves as confirmation of the clinical picture. The failure to find spirochetes in the tissue is disappointing, but it is a generally accepted fact that the demonstration of spirochetes in late syphilitic tissue is often impossible.

Ordinarily syphilis is considered a disease whose treatment is primarily medical. However, in the treatment of gastric syphilis surgery is frequently indicated. The differential diagnosis between syphilis and carcinoma, at times, is so difficult or impossible to make upon a clinical basis that resection of the lesion is indicated because it is the safest course to follow. Surgery is necessary in obstructing syphilitic lesions of the stomach because, as Beck[4] has pointed out, ''. . . no antisyphilitic therapy will be able to cure a cicatricial contraction . . . operation is the cure of mechanical obstruction.'' In accord with Beck are Allen,[5] LeWald,[6] and others. Graham,[7] in reviewing the literature, believes surgery for syphilis of the stomach is indicated when either bleeding, perforation, or obstruction is a complicating factor and concludes that resection of the pathologic tissue is the procedure of choice rather than some short-circuiting operation.

As antisyphilitic therapy may be relied upon to control the future advance of the disease, surgery's singular purpose is the control of the pathologic process at the time of surgical attack. Total gastrectomy is indicated only when the entire stomach is so involved in cellular infiltration and scarring that nothing short of total gastrectomy will remove the pathology. In the case reported here, complete gastrectomy was never considered before the abdomen was opened. As may be seen in Fig. 1 the dilatation of the abdominal esophagus was easily misinterpreted as the gastric fundus, and I felt that a subtotal gastrectomy would be relatively easy. However, when the pathology was actually seen, the total extirpation of the stomach was necessitated, for only after its removal was it mechanically possible to do an esophagojejunostomy.

The total gastrectomy as illustrated in Fig. 3*A*, *B*, *C*, and *D* was made simpler than usual by the elongation and dilatation of abdominal esophagus.

An enteroenterostomy between the loops of the jejunum was not done. Lahey[8] has pointed out that this procedure is not only unnecessary but undesirable in the majority of cases. If the anastomosis between the esophagus and jejunum is free and mobile, the proximal loop will empty satisfactorily. Furthermore, the proximal loop may dilate and at least

develop the function of holding a large portion of food which is one function of a stomach. It is also a sound physiologic principle to short-circuit bile and pancreatic secretions from as small a portion of the upper intestine as possible.

The maximal period of life following total gastrectomy, according to Walters,[2] has been four years and eight months. The question of how long it is possible for a patient whose stomach has been completely removed to live is as yet unsolved. Practically all total gastrectomies have been done for malignancies, and death in those upon whom operations have been successful has resulted from a recurrence of the malignancy. However, when total gastrectomy has been done for syphilis, the question of recurrence is eliminated and a more satisfactory answer to the question may be obtained. In a recent personal communication with Foster[9] he stated that the patient upon whom he did a total gastrectomy for syphilis[1] in 1926 was still living thirteen years and eight months after operation. She developed pernicious anemia four years after the operation, but the anemia has been satisfactorily controlled with the administration of ventriculin. This lends credence to the opinion that a person may maintain a surprisingly comfortable existence for an indefinite time without a stomach. Although my case has lived only seven and a half months to date, the ease with which nutrition is maintained is amazing, and it seems quite possible life and work may be carried on indefinitely particularly when regarded in the light of Poole and Foster's experience.

SUMMARY

1. What is considered the second case of syphilis of the stomach necessitating total gastrectomy is reported in detail and compared with the only previously reported case.

2. The diagnostic criteria and the surgical indications for surgery of gastric syphilis are reviewed.

3. The technique of total gastrectomy is illustrated and the importance of omitting a jejunojejunostomy is stressed.

4. Life may be maintained successfully for an indefinite time when total gastrectomy has been done for a benign lesion even though a severe degree of anemia develops. The anemia may be satisfactorily controlled by medical means.

Since this case report was submitted to the publishers, there has been an interesting follow-up on the patient:

He was readmitted to the John Gaston Hospital Jan. 9, 1941, sixteen months after operation, with lobar pneumonia. Response to sulfathiazol was prompt and recovery rapid.

His red blood cell count was 4,500,000 and the value for hemoglobin was 13.2 Gm.

He was eating three meals a day. Each meal consisted of an unrestricted food selection, and he could eat as large a quantity at one meal as he had ever done. He

had had no regurgitation of food for six months. His weight was 165 pounds, which represented a 50 pound gain since his operation.

X-ray studies revealed that the proximal loop of the jejunum had dilated to about two times normal size and was emptying normally.

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EPILOIA

Report of Cases

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EPILOIA is a clinical syndrome characterized usually by mental deterioration, epilepsy, adenoma sebaceum of the skin, and tuberous sclerosis of the brain. Other features inconstantly associated with the syndrome are benign tumors of the liver, spleen, kidney, heart, gastroenteric tract, retina, lung, thyroid, thymus, uterus, urinary bladder, and nail beds.

Sherlock[1] in 1911 coined the name epiloia for this remarkable clinical and pathologic entity. In England and in Europe approximately 1 per cent of the institutionalized epileptics and mental defectives suffer from this disease. In the United States the incidence of epiloia is reported to be but one-tenth as frequent. Hopwood,[2] for instance, found 5 cases of epiloia from a total of 4,000 records (0.1 per cent) at the Institution for Feebleminded, Orient, Ohio. Epiloia is described by Sherlock as a heredofamilial degeneration, and a family psychopathic history is sometimes obtainable. The occurrence of epiloia in one family through three generations has been reported by Kirpiznik[3] and in 5 of 9 siblings by Bouwdijk, Bastiaanse, and Landsteiner.[4] Fabing[5] reported the presence of epiloia in both of identical twins and, especially because of the mirror-image position of some of the skin and neurological lesions in his patients, concluded that the disease resulted from a defect in the zygote in its early life and that it was probably a truly hereditary (genotypical) disorder. Cockayne[6] states that epiloia is a dominant characteristic which appears to be very incomplete so that heterozygotes are sometimes indistinguishable from normal individuals. This would account for the number of isolated cases.

It is difficult to describe the clinical manifestations of epiloia due to the extreme variability in the symptomatology the individual patient may present. In general, however, the onset of the disease is manifest in infancy or early childhood. Mental deficiency is usually marked and developmental delay consequently is readily recognizable. Idiocy is a common finding. Epileptic seizures begin at an early age, but the type of attack is difficult to predict. One patient died in her first epileptic seizure at the age of 21 years. The facial lesions (adenoma sebaceum) become apparent within the first decade and abrupt development at the

Received for publication, June 26, 1940.

time of puberty is the usual sequence. Death occurs at an early age as a rule, but the mortality is in direct relationship to the extent of the mental deficiency, the development of the brain lesions, and the possible presence of visceral neoplasms. Incomplete or abortive forms of epiloia with the utmost variation in clinical findings exist and one must keep this fact constantly in mind in diagnosis.

Bourneville[7] in 1880 first described tuberous sclerosis or the main component of Sherlock's epiloia syndrome as a purely pathologic entity found at autopsy in young patients who had shown mental deficiency and epilepsy during life. The term "tuberous" Bourneville used to indicate the potato-like appearance of the sclerotic patches scattered throughout the cerebral cortex and ventricles of the brain. He regarded the cutaneous lesions (adenoma sebaceum) and the visceral neoplasms that he noted also in such patients as coincidental. The pathologic background of the disease has remained uncertain to the present day. Some authors favor a neoplastic process, some a vascular process, and still others maintain that it is a developmental anomaly. The brain lesions are found in the cortex and immediately beneath the ependyma projecting into the lateral ventricles. The tumors are present in multiple areas and the potato-like appearance is unmistakable. Microscopically, these tumors are composed of a neuroglial proliferation and remarkably large giant cells of glial origin (riesenzellen). Degenerative changes are manifest in many portions of the tumors.

The skin lesions of epiloia, the so-called adenoma sebaceum, were described and named by Pringle[8] in 1890. Adenoma sebaceum is a nodular eruption of red to brown color distributed over the face. The rash originates in the nasolabial folds and extends over the cheeks in butterfly pattern. Three types of adenoma sebaceum occur. The Pringle type of rash is red in color; the Balzer type is composed of pale nodules; and the third, the Hallopeau-Leredde type, is characterized by hard and wartlike nodules. Microscopically, adenoma sebaceum consists in a benign hyperplasia of the sebaceous glands. The red coloration of the Pringle type results from associated telangiectases. The hardness of the Hallopeau-Leredde type is due to excessive fibrous tissue proliferation.

Still other cutaneous lesions have been distinguished by various authors. Critchley and Earl[9] call particular attention to fibromas scattered over the trunk. Nevi, pigmentary disorders, vitiligo, hypertrichosis, cutaneous horns, white hair in the eyebrows, and pigmented and hairy moles are found in some instances. Nail-bed tumors in association with the syndrome of epiloia have been reported by Reitmann,[10] Hintz,[11] Fuhs,[12] Busch,[13] Elliot,[14] James,[15] and MacKenna.[16] These latter unusual but quite characteristic tumors were present in the entire series of cases presented here and are worthy of special consideration. They are filiform papillomas or fibromas and are located at the nail cutaneous juncture on

the fingers and toes. The size may vary from that of the small filiform-shaped tumor to the golf ball-sized tumor which we noted in two of the patients in our series of cases. In some instances the nail-bed tumors give rise to pain and discomfort and this is particularly true if secondary infection and hemorrhage occur. Microscopically the tumors are composed of a surface layer of heavily keratinized, stratified squamous epithelium. The underlying layer consists of a well-differentiated and sometimes hyalinized fibrous connective tissue in which an occasional fibroblast can be seen. The nails after a period of time undergo degenerative changes and become grooved. Chronic paronychia are not uncommon. Surgical removal is indicated if the tumors are giving rise to pain and discomfort or if hemorrhage and secondary infection have proved troublesome. In our experience the tumors do not tend to recur following adequate surgical removal.

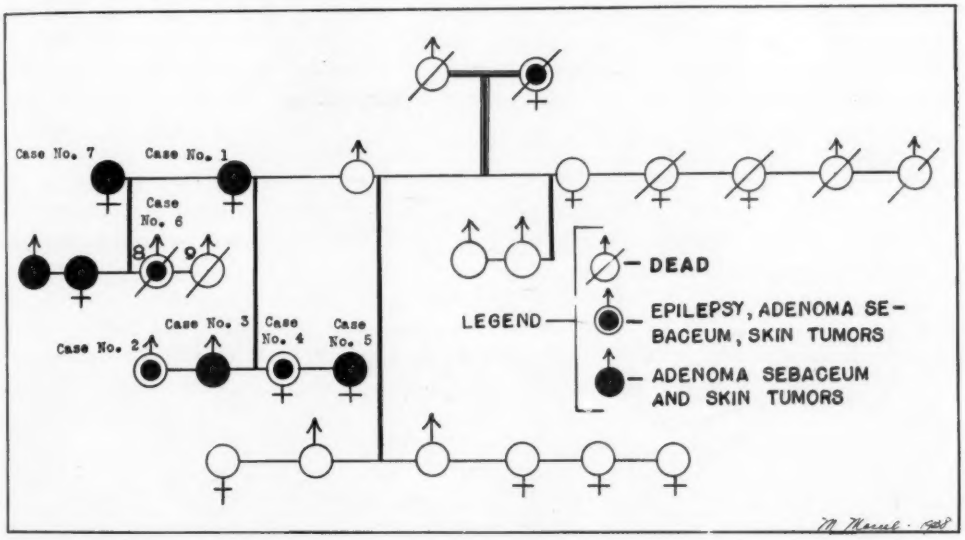

Fig. 1.—Genealogy of the epiloia family. Three generations are shown. The relative position in the family tree of the individual cases presented in this paper is indicated.

CASE REPORTS

Six members of one family in whom the diagnosis of epiloia has been established have come under our direct observation. Each of the six cases that we studied exhibited epiloia in more or less complete form. Post-mortem examination was performed in the seventh case. An attempt was made to determine the extent of the involvement by this disease in the family through three generations. Data relative to dead or absent members of the family were obtained by the careful examination of photographs and by history obtained from Mrs. H., the most intelligent member of the family at our disposal. Follow-up studies for a period of over two years have been carried out and observations relative to the progression of the disease are given with each case history.

The mother of the patients in Cases 1 and 7 and the grandmother of the patients in Cases 2, 3, 4, 5, and 6 died at the age of 33 years with pneumonia. According to her daughter, Mrs. H. (Case 1), she had petit mal attacks which began at the age of 18 years and had facial lesions similar to her own, as well as nail-bed tumors (Fig. 1).

CASE 1.—Mrs. M. H. (History No. 80902, Cincinnati General Hospital), a white female, 43 years of age, came to the Tumor Clinic of the Out-Patient Dispensary of the Cincinnati General Hospital in October, 1937, with the complaint of painful tumors on the fingers and toes. She had noted the presence of a small hard tumor under the nail of the third finger of the right hand at the age of 16 years. Similar growths had appeared at varying intervals since that time on the other fingers and toes. The tumors increased very slowly in size. This was particularly true of the growths on the toes, which were irritated by her shoes and which bled frequently. Infected ingrown nails likewise occurred at frequent intervals. Also, at the age of 16 years, or perhaps a short time later, the patient noted a papular eruption about the nose and face, which, while always present, seemed to have periods of exacerbation and remission. At the age of 34 years, however, she realized that the eruption about the face was definitely more pronounced and more extensive. No therapy for this condition was attempted. At the age of 38 years the tumors on the toes attained considerable proportions, and she had difficulty in wearing shoes and in walking. Hemorrhage from these tumors was severe on several occasions, and the patient "pared" the growths and applied iodine several times with transient relief of her symptoms. Past history was entirely negative. Her health had always been good. There was no history of headaches, vertigo, convulsions, or other type of neurological involvement. Her childhood and puberty apparently were uneventful. She had gone through the second year of high school and stated that she always got along well in school. She had been married twenty-four years and had four children. Her husband was living and well, and there was no apparent familial discord. She had many friends and adjusted herself well socially.

Physical examination was entirely negative except for the face, fingers, and toes. Height was 61 inches and weight, 137 pounds. On the face and nose there was a well-developed adenoma sebaceum of the Pringle type spread in typical butterfly pattern over the nasolabial folds and cheeks with one large discrete papillomatous growth at the base of the nose. Discrete, hard, gray to pink colored tumor masses were present at the nail cutaneous juncture of all the fingers and the toes. These tumors varied in size from that of a pea to a size slightly less than that of a golf ball. The larger tumors were on the toes and secondary infection in these neoplasms was the evident cause of her symptoms. The nails themselves were grooved. Neurological examination and spinal puncture were negative. According to the Stanford-Binet test, this patient had a mental age of 13 years 6 months with a resultant intelligence quotient of 84. She was, therefore, close to being of average intelligence. The opinion of the examiner was that she evidenced no deterioration in her mental abilities. Roentgenographic studies of the head, chest, and abdomen, including pyelograms, failed to reveal the presence of a visceral tumor.

The tumors on the toes were excised after secondary infection had cleared up. Microscopic examination of the neoplasms revealed a very thick keratinized surface layer of stratified squamous epithelium overlying a subcutaneous layer of cellular fibrous connective tissue. Several of the tumors prior to surgery were treated with radium and x-ray to determine radiation sensitivity. No response to this treatment was obtained.

This patient now has been followed over a period of two years. No change in the mental status has occurred. The nail bed tumors have not recurred. There is still no evidence of visceral neoplasm (Figs. 2 and 3).

CASE 2.—L. H. was a white male, 22 years of age, the oldest son of Mrs. M. H. (Case 1). According to the history obtained from his mother, he had been subject to epileptic attacks of grand mal type since 1 year old. This boy showed marked mental deterioration. He was an inmate of the State Home for Epileptics

Fig. 2.—Case 1, 1938. The facial lesion of epiloia, adenoma sebaceum, is well illustrated.

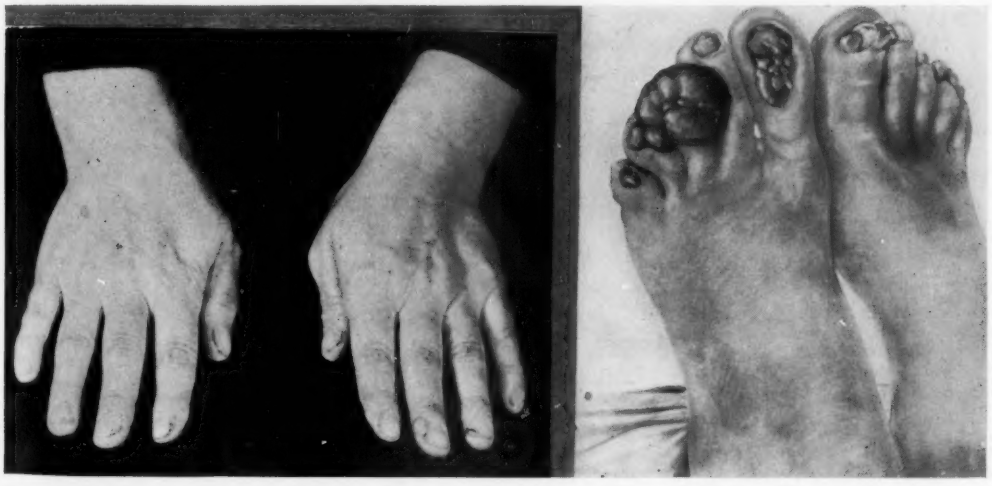

Fig. 3.—Case 1. The nail-bed lesions of the fingers and toes which are present in the entire series of cases are best illustrated in this epiloia patient.

at Gallipolis, Ohio, and he was able to perform simple manual tasks. Physical examination revealed a well-developed adenoma sebaceum of the Pringle type spread over the face in typical butterfly arrangement. There were numerous moles and wartlike growths distributed over the neck and trunk. The nails of the fingers and toes were grooved, and there were a small, hard tumor present in the nail bed of

the third finger of the left hand and numerous tumors of the nail beds on all the toes. These latter neoplasms were quite small in size and never had occasioned the patient any difficulty by their presence.

Neurological examination when first made in 1937 gave no positive findings with the exception of a marked tache cerebrale and a nonsustained fibrillary nystagmus on lateral fixation. Within the previous two years he had developed a left facial hemiatrophy and ptosis of the lower left eyelid. The significance of these neurological findings was not determinable. He had a mental age of 7.6 years with an intelligence quotient of 49. His epileptic attacks occurred for the most part during the night. There has been little or no progression in the size of the nail bed tumors within the two-year period that he has been under our observation (Fig. 4).

CASE 3.—R. H. (History No. 83453, Cincinnati General Hospital), was a white male, 21 years of age, the second son chronologically of Mrs. M. H. (Case 1). The past history was entirely negative except that apparently he was subject to some type of epileptic seizures during infancy. He attended a school for the mentally retarded, and at the age of 16 years dropped out, having reached the

Fig. 4.—Case 2. The nail-bed tumors of this epiloia patient are well developed.

fifth grade. According to the Stanford-Binet test in 1937, he had a mental age of 8 years 10 months, with a resultant intelligence quotient of 55. He was, therefore, definitely mentally retarded. He was tested at the Vocation Bureau on Jan. 6, 1926, when he was 7 years old. His mental age then was 4 years 10 months, and his intelligence quotient was 69. He was tested again at the Vocation Bureau on Sept. 11, 1933, when he was 14 years 8 months old. At that time he had a mental age of 8 years 10 months with intelligence quotient of 60.

Physical examination revealed a stupid appearing individual of 21 years. A well-developed adenoma sebaceum of the Pringle type was present on the face. Multiple papillomatous growths were noted on the neck and shoulders. Café au lait patches were present on the face, thorax, and abdomen. Nail-bed tumors of small size were present on all the toes and the third and fifth fingers of the right hand. Repeated neurological examinations of this patient were negative. The nail bed tumors were excised surgically and no recurrence was detectable. Microscopically these tumors had the same structure as those removed from the patient in Case 1. X-ray studies of this patient were entirely negative.

CASE 4.—V. H. (History No. 5030, Cincinnati General Hospital), was a white female, 16 years of age, the third child of Mrs. M. H. (Case 1). She was an

idiot and had had epileptic seizures of grand mal type since the age of 5 months. She also was an inmate of the State Home for Epileptics at Gallipolis, Ohio. She was totally unable to care for herself and was animal-like in appearance. She mumbled constantly to herself in an indistinguishable tone of voice as she rocked herself back and forth with accompanying athetoid movements of the forearms and hands. Adenoma sebaceum was present but poorly developed. The nails were grooved with a minute nail-bed tumor on the fifth finger of the right hand. There were numerous keloid scars scattered over the body. Neurological examination when first made in 1937 was completely negative except for the athetoid movements. Re-examination in January, 1940, revealed several findings: slight weakness of the right side of the face, deep reflexes on the right more active than on the left, and the right side more spastic generally than the left. She constantly tended to assume a scissors position of the legs. In 1931 following study at the Cincinnati General Hospital and the Jewish Hospital of Cincinnati, an exploratory craniotomy was performed. Diffuse sclerotic patches were found scattered over the cortex. The diagnosis of an inoperable brain tumor, probably a glioma, was made. X-ray studies are not obtainable.

CASE 5.—J. H. (History No. 52153, Cincinnati General Hospital), was a white female, 14 years of age, the fourth child of Mrs. M. H. (Case 1). She was of average intelligence and had reached the first year of high school. Adenoma sebaceum was detectable on the face. There were small cutaneous nevi on the abdomen and extremities. Nail-bed tumors were present on the fifth finger of the right hand and the fourth toe of the left foot. Neurological examination was negative. There was no history of epilepsy. X-ray studies were entirely negative.

CASE 6.—L. W. was the third child of the sister of Mrs. M. H. (Case 1) and the first cousin of the patients in Cases 2, 3, 4, and 5. He was subject to epileptic seizures of grand mal type from infancy. He died in 1930 at the age of 5 years. At the time of death he was under the care of a private physician who made the diagnosis of a brain tumor. No further record was available. An autopsy was performed, and the diagnosis of a brain tumor of a glial type was made. The post-mortem examination was limited to the head. Fortunately the brain was saved. In a pathologic report dated June 14, 1930, Dr. Pearl Zeek, of the Pathologic Department of the Cincinnati General Hospital, made the following observations: "The specimen consists of a brain removed from a child about 5 years old. The brain tissue is extremely soft and cannot be completely examined until further fixation has taken place. However, there is marked asymmetry of the two cerebral hemispheres and on a partial horizontal incision beginning at the frontal pole a large soft mass resembling neoplastic tissue rolled out of the lateral ventricle. This tissue shows yellowish pigmentation in places and is extensively necrotic and blood stained. There is no evidence of meningitis. Diagnosis: Brain tumor, possibly a glioma." Microscopic study was not done at the time.

This brain, which had been preserved in Kaiserling's solution, was re-examined by Dr. Charles Aring, of the Neuropathology Department, University of Cincinnati, who in 1938 made the following report: "The entire brain is of soft consistency and one cannot make an accurate description of the cortex as the sulci have been flattened and softened, due to many years of storage. Through and through sections have been made of the cerebral hemispheres. The lateral ventricles are tremendously dilated and filled with tumor masses of cheesy consistency. These masses are now 2 to 8 cm. in length and 1 to 5 cm. in breadth and width. Microscopic examination shows these tumors to be composed of cells of large size and rather uniform outline. Blood vessels are numerous. The stroma of the tumor is marked and is probably made up of the processes of the cells. The cells vary in size and

some of them reach enormous proportions. The nuclei stain deeply, are irregularly shaped, and are placed at the periphery of the cell. Many of the cells are multinucleated. No mitoses are seen.

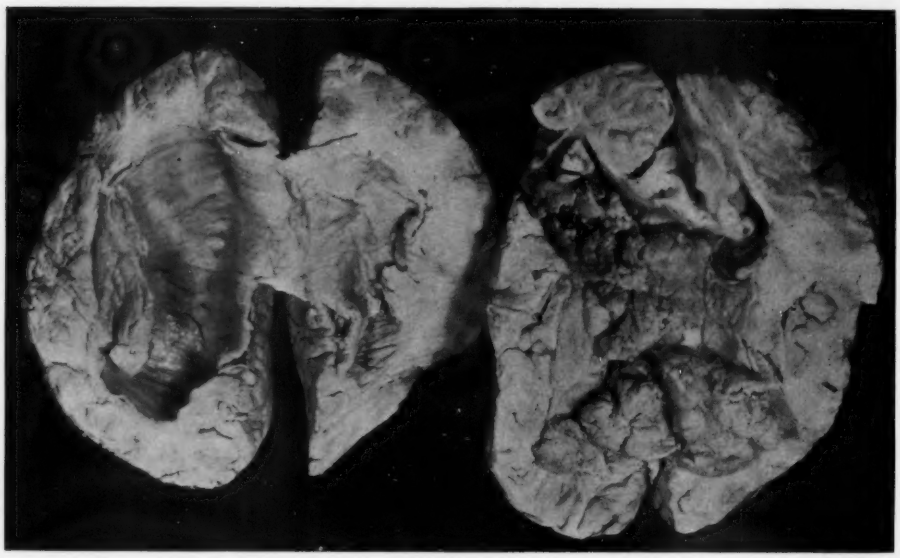

Fig. 5.—Case 6. Hemisection of the brain illustrating the tuberous masses filling the ventricles as described by Bourneville.

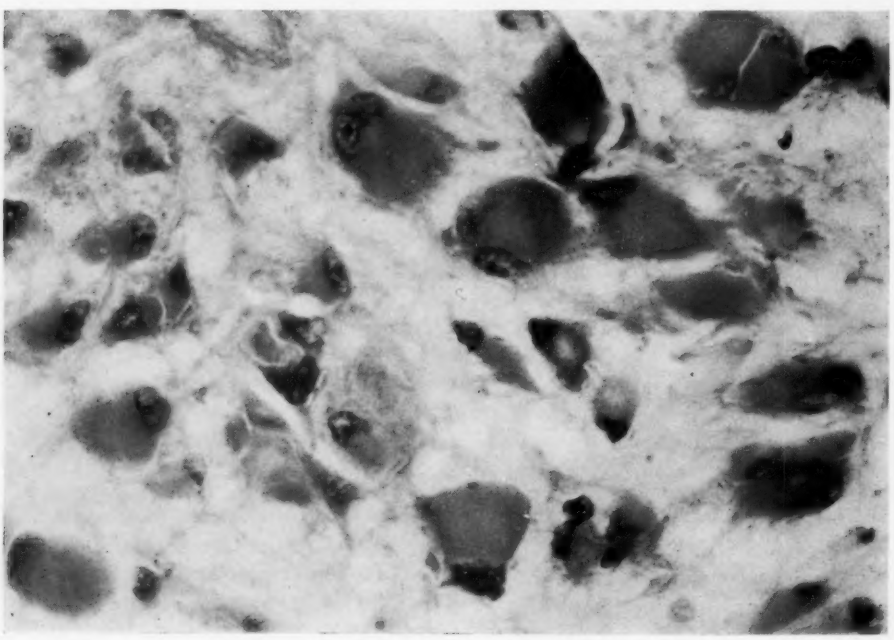

Fig. 6.—Case 6. High-power view of section through brain tumor. The giant cells, characteristic of tuberous sclerosis, are well illustrated.

"Study of sections taken from the cerebral cortex shows complete cytoarchitectonic disorganization. Large cells which appear similar to those described previously are scattered through the widened cortical layers. In some locations

there are veritable nests of giant cells. There are patchy areas of demyelinization in the vicinity of the nests of cells in the white matter of the cerebral cortex. In some places this demyelinization is present in an entire gyrus. . . . Diagnosis: Tuberous sclerosis.'' (Figs. 5 and 6.)

CASE 7.—Mrs. W. was a 47-year-old white female, the mother of L. W. (Case 6) and the sister of Mrs. M. H. (Case 1). She was unwilling to submit to examination, photography, or other type of special workup. She was subject to petit mal seizures which she referred to as ''trembling spells.'' A well-developed adenoma sebaceum of the Pringle type was present on the face and nose. Nail-bed tumors which varied from filiform papilloma to golf ball-sized neoplasms were present on the fingers and toes. Secondary infection had occurred in several of the tumors of the toes. Hemorrhage from the tumors had occurred on numerous occasions. The nails themselves were grooved, and chronic paronychias were distinguishable.

COMMENT

Although the mother of Cases 1 and 7 (the grandmother of Cases 2 to 6) was not examined clinically, the history of epileptic seizures, adenoma sebaceum, and nail-bed tumors in this woman make the diagnosis of epiloia in her case a valid presumption. If this is granted, the foregoing study reveals the direct passage of the disease through three generations.

The study discloses that, if the epiloia patient lives through puberty and is capable of mating, transmission of the disease is possible. Undoubtedly the reason for so few examples of this type of transmission in the literature lies in the fact that the average patient with epiloia is so mentally and physically incapacitated at puberty that marriage and mating cannot occur.

Study of the family tree discloses that one daughter (Case 1) of the original epiloia patient transmitted the disease in all its intensity to all four of her children who lived to puberty; whereas, the other daughter (Case 7), who shows signs of the disease, apparently did not pass it on to her two older children. This reveals the undoubtedly complex nature of the transmission. In the instance of the other two children of the original epiloia patient who had issue, there is no evidence of the disease. It is not found in their children as well. This suggests that the disease is not a recessive characteristic but rather a dominant characteristic which tends to be incomplete, as Cockayne[6] contends.

The nail-bed tumors, an uncommon accompaniment of the epiloia syndrome, are worthy of notice because of their consistent presence throughout the entire series of cases. The presumption here is that epiloia is transmitted even in its minute details.

Last, the direct transmission of the disease from parent to offspring through three generations, as presented by this study as well as that of Kirpiznik,[3] proves that the syndrome is truly hereditary, i.e., genotypical, as suggested by Fabing[5] in his study of the disease in identical twins.

SUMMARY

1. The syndrome of epiloia is described.

2. A family tree is outlined in which the disease seemed to appear in three generations.

3. Seven case histories are outlined.

4. The presence of nail-bed tumors, an unusual accompaniment of the syndrome, is noted throughout the group.

5. The contention is advanced that, if the patient with epiloia lives beyond puberty with reasonably good mental and physical health, he or she may transmit the disease to the next generation.

6. The study is offered as proof of the truly hereditary or genotypical transmission of the disease.

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A SYSTEM OF SURGICAL FOLLOW-UP AND RECORD KEEPING

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TO LOCATE, assemble, and peruse a large number of hospital records is such a laborious duty that few have the time or patience necessary for such a task. As a result, every hospital record room contains a wealth of clinical data which lie hopelessly buried beneath the technical difficulties of bringing them to light. In order to facilitate the collection of clinical data from the records of hospital admissions and return visits and, at the same time, to furnish a system of follow-up on all hospital cases, a procedure has been established on the Surgical Service of the Duke Hospital which has proved itself to be quite satisfactory.

The system of follow-up and record keeping is set up about one file which contains a follow-up sheet (Fig. 1) for each patient operated upon. On this sheet is recorded a brief abstract of all the pertinent findings in the hospital course. On this sheet also is subsequently recorded an abstract of each follow-up visit. These sheets filed chronologically according to operation bring together in one folder all the hospital and follow-up data on each group of operative cases. With them the department is able to summon each group of cases systematically for follow-up. In addition, the department is able to give statistical information easily and quickly at any time concerning the hospital record, the immediate hospital mortality, and the follow-up results in each group of cases operated upon.

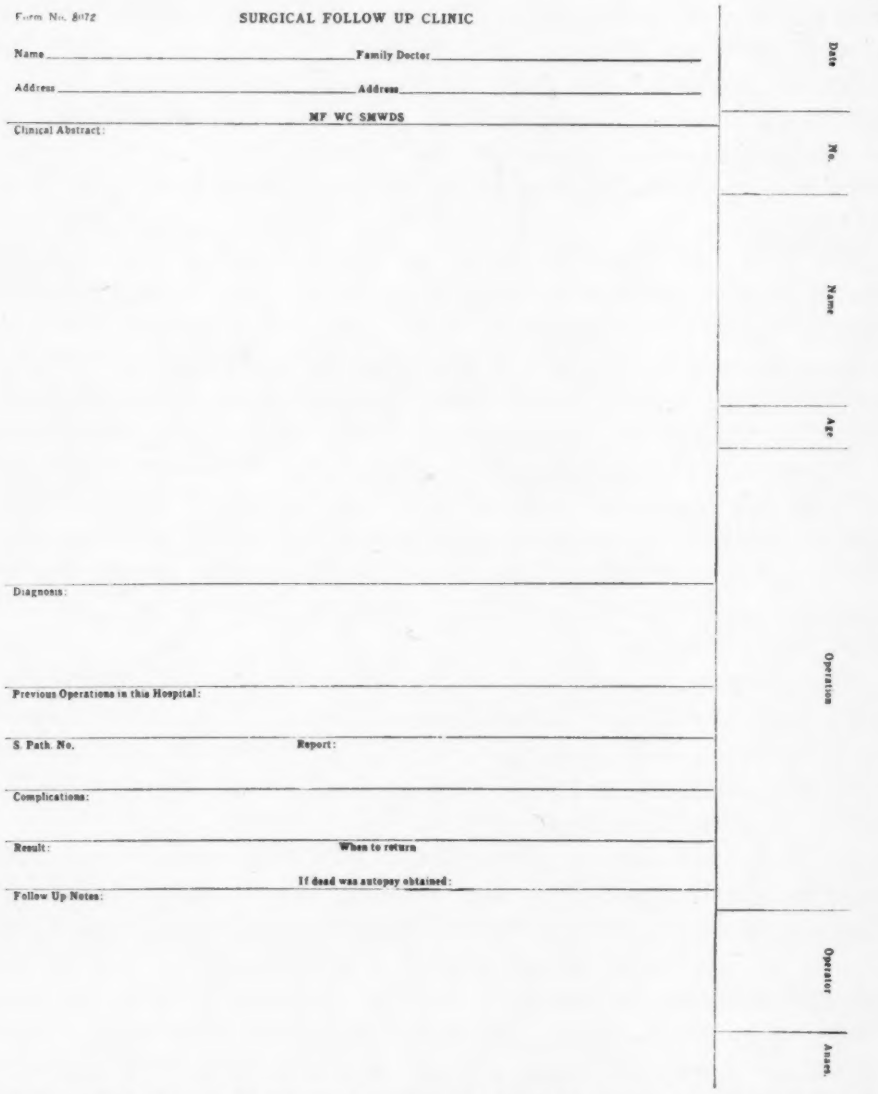
The follow-up clinic is staffed by one full-time secretary. Clinic data are accumulated in one file, containing a follow-up sheet for each patient operated upon, and one book in which are compiled by year and by total hospital experience the immediate hospital mortality and the follow-up results on each group of cases.

The follow-up sheet, which is filled out for each patient, is an eight and one-half by eleven inch sheet of heavy twenty-eight pound ledger paper on which a basic form for the follow-up clinic is printed, as in Fig. 1. In the space for clinical abstract a brief account of the history, physical examination, laboratory findings, operative findings, and post-operative course is recorded. In certain of the more frequent conditions which are of especial interest a special form is printed in the space for clinical abstract (Fig. 2). Such forms are used for diseases of the

Received for publication, July 5, 1940.

appendix, biliary tract, breast, thyroid, stomach, and colon and for thoracoplasties. These forms are checked at history meetings, and, being filled out in full, they insure complete recording of all pertinent data.

The follow-up sheet is filled in by the clinical clerk or by the intern on the ward. When the patient is discharged from the hospital, his record passes over the resident surgeon's desk. Here the hospital record is diagnosed and the follow-up sheet is checked to see that it is complete and then is removed from the record. The follow-up sheet is then coded according to operation and sent to the follow-up clinic for filing, which is done according to a classification of the operations done by the general surgical staff.


Form No. 8072

SURGICAL FOLLOW UP CLINIC

Name _____ Family Doctor _____

Address _____ Address _____

MF WC SMWDS

Clinical Abstract:

Diagnosis:

Previous Operations in this Hospital:

S. Path. No. Report:

Complications:

Result: When to return

If dead was autopsy obtained:

Follow Up Notes:

Date

No.

Name

Age

Operation

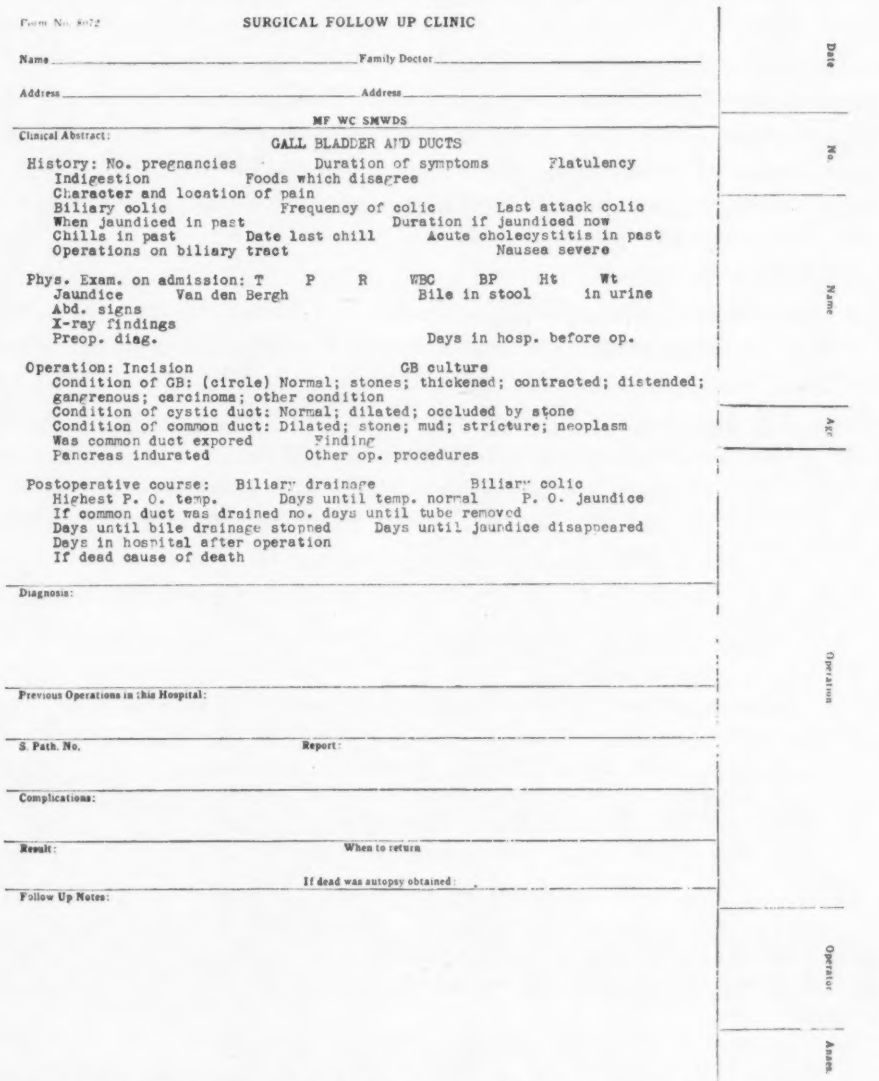
Operator

Anaes.

Fig. 1.—The basic form for the follow-up sheet. In the space for clinical abstract pertinent facts in the history, physical examination, laboratory findings, operative findings, and postoperative course are recorded under separate paragraphs.

When each patient returns for check-up examination, and on every subsequent follow-up visit, notes on his condition are transcribed onto the follow-up sheet. Information on the follow-up sheet is thus kept constantly up to date. These data are transferred to the follow-up sheet by the department secretary who inspects the unit history of every patient making a return visit to the hospital each day. She keeps out those cases treated on the surgical service and abstracts the note made in the clinic on the follow-up sheet.

When the follow-up department was first organized in 1937, it did not contain the operations of the preceding seven years dating back to the opening of the hospital in July, 1930. A sheet for each of these



Form No. 8072 SURGICAL FOLLOW UP CLINIC

Name _____ Family Doctor _____

Address _____ Address _____

MF WC SMWDS

Clinical Abstract:

GALL BLADDER AND DUCTS

History: No. pregnancies Duration of symptoms Flatulency
Indigestion Foods which disagree
Character and location of pain
Biliary colic Frequency of colic Last attack colic
When jaundiced in past Duration if jaundiced now
Chills in past Date last chill Acute cholecystitis in past
Operations on biliary tract Nausea severe

Phys. Exam. on admission: T P R WBC BP Ht Wt
Jaundice Van den Bergh Bile in stool in urine
Abd. signs
X-ray findings
Preop. diag. Days in hosp. before op.

Operation: Incision GB culture
Condition of GB: (circle) Normal; stones; thickened; contracted; distended; gangrenous; carcinoma; other condition
Condition of cystic duct: Normal; dilated; occluded by stone
Condition of common duct: Dilated; stone; mud; stricture; neoplasm
Was common duct expored Finding
Pancreas indurated Other op. procedures

Postoperative course: Biliary drainage Biliary colic
Highest P. O. temp. Days until temp. normal P. O. jaundice
If common duct was drained no. days until tube removed
Days until bile drainage stopped Days until jaundice disappeared
Days in hospital after operation
If dead cause of death

Diagnosis:

Previous Operations in this Hospital:

S. Path. No. Report:

Complications:

Result: When to return

If dead was autopsy obtained:

Follow Up Notes:

Date
No.
Name
Age
Operation
Operator
Anes.

Fig. 2.—The special form of the follow-up sheet used for gall bladder operations. Special forms have also been prepared for diseases of the appendix, breast, thyroid, stomach, and colon and for thoracoplasties.

operations was prepared, however, from the data available in the files of the operating room. Information available from this source was sufficient only to fill in the data along the vertical column on the right side of each follow-up sheet (Fig. 1). To complete the sheet, it was necessary to obtain the unit history of each case and record the pertinent data. This work has been done by a group of students employed under the NYA. In some groups of cases no effort has been made to fill out the clinical abstract. In those of interest for follow-up purposes, however, the entire follow-up sheet has been completed for all the early cases.

METHOD OF FOLLOW-UP

A specific month each year is set aside in which to follow each group of cases. Thus, stomach operations are followed in October, colon cases in November, thyroid cases in December, gall bladder cases in January, appendix cases in February, hernia cases in March, rectal cases in April, chest cases in May, breast cases in June, and miscellaneous conditions in July, August, and September. All cases with malignant tumors, peptic ulcers, or pulmonary tuberculosis are followed yearly. Remaining cases with a few exceptions are followed yearly for three years and then every five years.

A form letter is prepared for each group of cases followed. The following is a form letter used in follow-up of gall bladder operations. Similar forms are prepared for each operative procedure.

We are very much interested in knowing how you have been getting along since your gall bladder operation at the Duke Hospital, and should appreciate it very much if you would answer the questions below. The answers may be written in the space following each question and the letter returned to us in the enclosed envelope, which requires no stamp.

1. Do you believe yourself to be cured, improved or unimproved by the operation?
2. Have you had any gall bladder colic since operation? If so, when and how often?
3. Have you been jaundiced since the operation? If so, when and how often?
4. Do you have any indigestion? Describe it.
5. Are you less constipated, more constipated, or has there been no change in bowel movements since operation?
6. If you have moved, what is your new address?

If you feel that your symptoms have not been relieved, we would like to have you return to the Clinic for re-examination. The enclosed card, presented at the Clinic entrance any afternoon, except Saturday and Sunday, at 1:00 P.M., will entitle you to examination without charge, if you come before the date stamped on the card.

Looking forward to hearing from you promptly, I am,

Sincerely yours,

Surgical Follow Up Clinic.

This form letter is mailed to each patient in the group, being sent by first class mail. If the letter is not answered and is not returned, it is assumed that it has been received but ignored and a second similar letter is sent ten days later. If the second letter is ignored, a third is sent ten days after the second. If no answer is received from these letters or if the first letter has been returned marked unknown, moved, etc., letters are written to relatives, the family doctor, or the local welfare agency in an effort to locate the patient. Each letter contains a business reply envelop which requires no stamp which the patient is asked to use in returning answers to the questionnaire. Each letter also contains a card admitting the patient to the clinic without charge for check-up examination, if the visit is made in the month specified for the follow-up.

It has been our experience that 45 per cent of patients will respond to the first letter, another 23 per cent to the second, and 14 per cent to the third. Letters to the family doctors, relatives or welfare agencies are successful in locating another 10 per cent. In about 7 per cent of our cases no follow-up has been possible and we have had to record such patients as lost.

The problem involved in follow-up at the Duke Hospital is complicated by the fact that the hospital serves a rural community whose average patient comes a distance of seventy-seven miles. Only 22 per cent of patients come from Durham. Of the patients admitted, 86.8 per cent are charity or part pay patients and 16 per cent are negroes who shift their residence frequently. For economic reasons, it is frequently difficult for our patients to present themselves at the clinic for re-examination. If such is the case in patients whose symptoms continue, the patient's local doctor is asked to submit data concerning him.

Under this system, we have been able to obtain a satisfactory follow-up in 92.5 per cent of our large operative cases (Table I) operated upon from the time the hospital opened in 1930 until the present. A follow-up is much more successful if patients are followed promptly and regularly. As shown in Table II, we have been unsuccessful in tracing 18 per cent of our patients operated upon the first year the hospital was open, no effort being made to locate these patients until eight years had

TABLE I

NUMBER OF PATIENTS FOLLOWED

OPERATION	NO. PATIENTS DISCHARGED	NO. PATIENTS FOLLOWED	PERCENTAGE FOLLOWED
Stomach operations	209	194	92.8
Colon operations	103	94	91.2
Radical mastectomy	173	163	94.2
Thyroid operations	396	367	92.6
Gall bladder operations	405	371	91.3
Total	1,286	1,189	92.5

TABLE II

PERCENTAGE OF PATIENTS LOST TO FOLLOW-UP IN 1940
TABULATED BY YEAR OF OPERATION

YEAR	PERCENTAGE OF PATIENTS LOST TO FOLLOW-UP
1930-31	18.0
1931-32	13.0
1932-33	16.3
1933-34	10.1
1934-35	10.0
1935-36	5.4
1936-37	7.6
1937-38	3.2
1938-39	0.5

elapsed following their discharge from the hospital. On the other hand, in the group operated upon in the past three years since the follow-up clinic has been in existence only 3.7 per cent of a total of 608 patients have been lost.

Tabulation of immediate hospital mortalities is compiled yearly and for the total hospital experience for each group of cases. These data are filled in on a special form and bound in a loose-leaf book. In the same book are also tabulated each year the follow-up results on each group of cases.

Annual reports are furnished the head of the surgical department giving the hospital mortality for the year and for the total hospital experience and the follow-up results on each group of cases operated upon on the general surgical service. These results are discussed in staff conference. Data from the abstracts of hospital records and follow-up visits is always immediately accessible to any member of the staff. Special studies from groups of cases of their choosing are done by house officers and discussed at staff meeting frequently during the course of the year.

SUMMARY AND CONCLUSIONS

1. Clinical material in the records of hospital cases must be made easily available if it is to be utilized.

2. A systematic and sustained effort to follow end results in old patients is necessary if need for change is to be recognized and progress in surgery is to be made.

3. A method of surgical follow-up and record keeping is presented which:

a. Gives a satisfactory follow-up in 92.5 per cent of large operative cases over a nine-year period.

b. Makes information from the hospital record and follow-up visits of every group of operative cases easily and immediately accessible.

c. Enables members of the department of surgery to keep in constant touch with immediate and late results in all operative cases.

d. Enables the department to recognize and to alter promptly surgical practices or procedures whose results are not satisfactory.

SUCCESSFUL LIGATION OF A PATENT DUCTUS ARTERIOSUS

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A REVIEW of the literature prior to 1939 on persistent patent ductus arteriosus shows that a thorough study of the anomaly has been made with regard to frequency, probable origin, clinical symptoms and signs, course, and complications, but that there is an almost complete lack of suggestions for treatment.

Munro[1] (1907) and, later, Graybiel, Strieder, and Boyer[2] (1938) recognized the possibility of surgical correction of this condition. The latter group should be given credit for their attempt at ligation although it was unsuccessful; it should also be noted that their patient had a complicating bacterial endarteritis. In 1938 Gross and Hubbard[3, 4] devised and executed a transpleural operation, which, so far, seems adequate in uncomplicated cases. These authors have reported four ligations without a death. Recently (1940) Jones, Dolley, and Bullock[5] have contributed an interesting report of seven ligations, all successfully accomplished by the technique described by Gross. Although one of these patients died later, the death could not be attributed to the surgical procedure.

We report here another successful ligation of a patent ductus arteriosus by the transpleural technique of Gross, feeling that all such operations should be recorded so that the proper evaluation may be placed upon the results of this procedure.

Case Report.—Miss C. B., a white female, aged 20 years, was admitted to the Charity Hospital on July 20, 1939, for correction of a disabling contracture of the left foot. The corrective operation was performed on Aug. 4, 1939, and recovery was uneventful.

During the routine examination of the patient, the intern, Dr. I. Redler, detected the physical signs of a patent ductus arteriosus and correctly diagnosed the presence of this anomaly, which had also been recognized by Dr. Richard Ashman in 1933 when he examined the patient at the Heart Station of the Charity Hospital.

The patient gave a history of heart trouble since infancy. As a baby she had convulsions which were associated with cyanosis of the lips and face. She had matured slowly and was moderately deaf. She experienced dyspnea and palpitation on slight exertion, but these symptoms had not prevented her from carrying on the usual activities of childhood.

On physical examination the patient was noted to be small in stature and subnormal in development. Physically and mentally she seemed like a 12-year-old child. She presented the physical signs of a widely patent ductus arteriosus without com-

Received for publication, July 8, 1940.

plicating lesions: collapsing pulse of large volume; blood pressure, 130/65; throbbing carotids; and continuous thrill and murmur with systolic accentuation. Both thrill and murmur were widely distributed but were most intense in the second left intercostal space near the border of the sternum. The apex beat was diffuse and forcible but was displaced only slightly to the left. There was neither cyanosis nor clubbing of the fingers.

X-ray films of the chest revealed moderate enlargement of the heart, marked prominence of the pulmonary conus, and a small aortic knob.

An electrocardiogram (Fig. 1), unchanged from one taken in 1933, showed a deep notch on the downstroke of R-1, a definite Q-wave in Leads II and III, and prolongation of the RST interval. The electrocardiogram was not considered definitely abnormal. It was suggested that the unusual form of the QRS might be due to some associated anomaly, such as a defect of the interventricular septum. The blood count and urinalysis were normal.

Operation was decided upon for the following reasons: (1) Obviously the ductus arteriosus was widely patent. (2) It was fairly certain that no other serious anomalies, for which the patency of the ductus might be compensatory, were present. (3) Cardiac enlargement, indicating overwork of the heart and possible future cardiac failure, was present. (4) The patient seemed to be a good surgical risk.

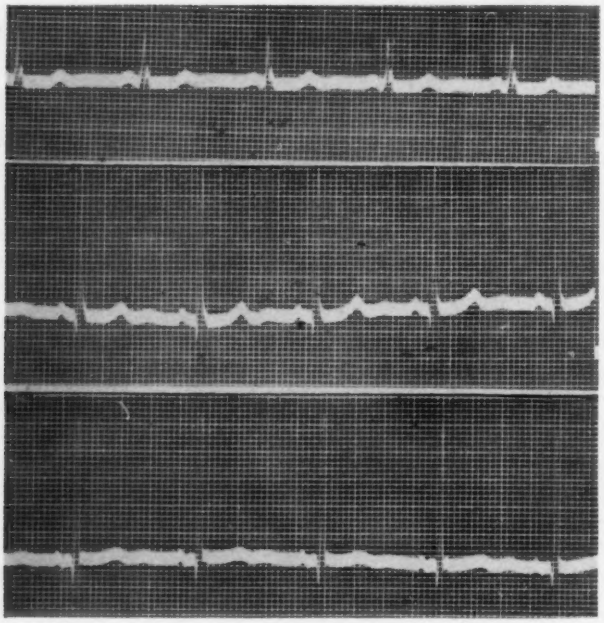

Fig. 1.—Electrocardiogram taken one week before operation (patient C. B. sitting).

Artificial pneumothorax was induced to prevent the consequences of sudden collapse of the left lung at operation. On Sept. 26, 27, 28, and 30 from 300 to 400 c.c. of air were given and the highest reading obtained was + 1.5 on expiration.

Operation was performed on Oct. 2, 1939, under cyclopropane anesthesia. An incision was made in the third interspace, the third costal cartilage was divided, and the third rib was displaced upward. After opening and reflecting the mediastinal pleura, the pulmonary artery was found to be dilated and the walls appeared to be thickened. A distinct continuous thrill was palpable as the pulmonary artery was dissected away from the aortic arch. The ductus was located by applying digital pressure at various levels between the arch and the pulmonary artery until

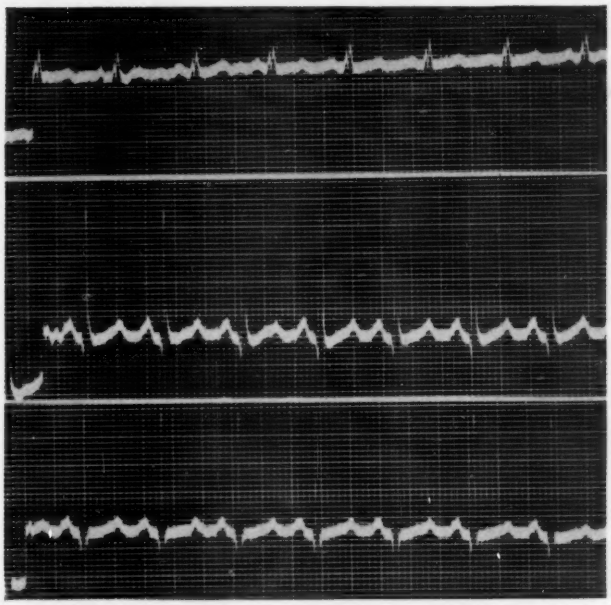

Fig. 2.—Electrocardiogram made immediately after operation. Shift of electrical axis to right, probably due to change in position of heart (patient C. B. recumbent).

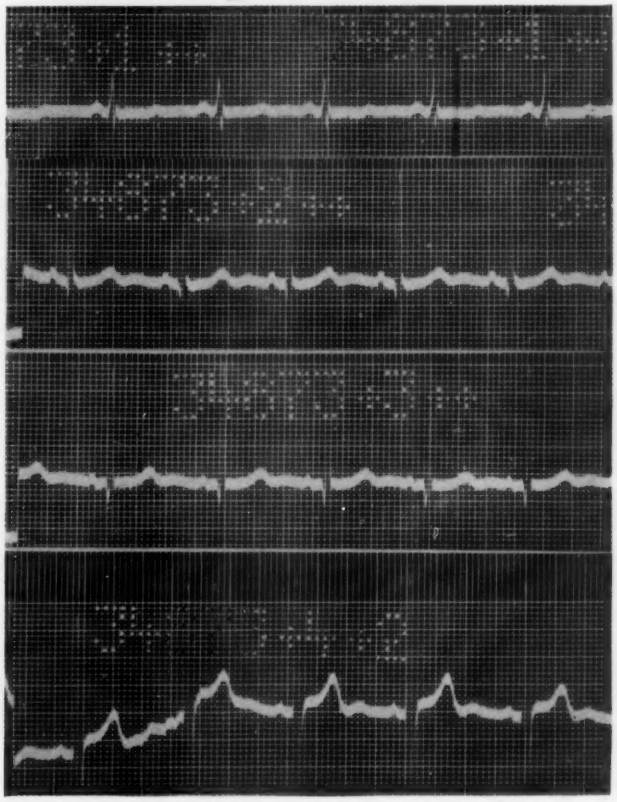

Fig. 3.—Electrocardiogram taken two weeks after operation. T-wave slightly lower than in preoperative tracing (patient C. B. sitting).

the thrill disappeared. At the same instant the murmur also disappeared and the diastolic pressure rose from 60 to 80 mm. On releasing the digital pressure, all abnormal signs returned. The ductus was then carefully dissected and was found to be about 12 mm. in length and 8 mm. in diameter. It was ligated at both ends with No. 8 braided silk. The pleura was closed with interrupted silk sutures and the chest wall was closed in layers with interrupted chromic No. 2 sutures. Linen was used for the skin. The left arm was strapped to the chest.

An electrocardiographic tracing made immediately after operation (Fig. 2) showed R-1 and T-1 lower than in the previous electrocardiogram, probably due to the difference in position of the heart. Depression of RST segments in Leads II and III was attributed to the presence of an auricular T-wave.

Fig. 4.—Patient C. B. seven months after operation.

The patient was returned to her bed in excellent condition. Carbon dioxide inhalations were administered every three hours, first as a routine measure, and later because they seemed to benefit the patient.

On the afternoon of the first postoperative day a pericardial friction rub was audible along the left border of the sternum but had disappeared by the afternoon of the next day. This rub was probably due to a small amount of bleeding into the mediastinum.

There was an elevation in temperature to 102° on the second postoperative day and a daily afternoon rise for six days thereafter ranging between 99 and 100°. No special postoperative care was indicated.

During convalescence the blood pressure remained fairly constant, from 120/80 to 126/86, the systolic pressure being lower and the diastolic pressure higher than the preoperative levels. The pulse had lost its Corrigan-like character. The thrill and continuous murmur were no longer present but were replaced by a systolic murmur of moderate intensity heard only in the second left interspace.

The sutures were removed on the eighth postoperative day and the patient was allowed to get out of bed.

An x-ray picture taken Oct. 15, thirteen days after operation, showed no change in the cardiac silhouette, the left lung being almost completely re-expanded at that time.

An electrocardiogram made Oct. 17 (Fig. 3) was essentially the same as the tracing made preoperatively.

The patient was discharged from the hospital on Oct. 20, 1939. Since then she has been examined several times, the last time having been on Nov. 14, 1940 (Fig. 4).

On each occasion the physical findings have been essentially the same as those present when she left the hospital. The x-ray picture is unchanged. There is a persistent systolic murmur, which we attribute to dilatation of the pulmonary artery. The patient has returned to her part-time position in an NYA sewing project and reports that, so far as she can tell, she is no better and no worse than before the operation. She feels well but is still made dyspneic by moderate exertion.

SUMMARY

The successful ligation, according to the technique described by Gross and Hubbard, of a patent ductus arteriosus in a 20-year-old white female is reported.

Seven months after the operation the patient's status is approximately the same except that there is no evidence of patency of the ductus. The patient may be spared the later development of heart failure, vegetative endarteritis, or other complications of this anomaly.

Supplementary Note.—Since the foregoing report was submitted for publication, the authors have had occasion to treat a second patient; unfortunately, fatal hemorrhage occurred in this instance. We report the case briefly because of the technical difficulty encountered after the major part of the operation had been completed.

N. M., a colored male, aged 12 years, was admitted to Charity Hospital on Feb. 27, 1940, with unmistakable clinical, x-ray, and electrocardiographic signs of persistent patent ductus arteriosus.

Operation was performed on July 19, 1940. A ductus about 1 cm. in diameter and approximately 1 cm. long was easily located. Obliteration of the ductus by digital pressure caused the diastolic pressure to rise from 50 to 84 mm., and also caused an immediate cessation of the thrill. All important anatomical structures were carefully identified and isolated with no particular difficulty. The left wall and the anterior and posterior walls of the ductus were cleared quickly, but in separating the right wall from the bronchus, dense connective tissue was found. The ductus was grasped with plain forceps and gentle traction was exerted, care being maintained not to injure the pulmonary artery. A right-angled cystic duct clamp was being used to separate the wall of the ductus from the bronchus when a stream of arterial blood was noticed. In the belief that the ductus itself had been injured, clamps were placed at the aortic and pulmonic ends. There was a gush of arterial blood which could not be checked except by clamping the aorta itself. Death quickly followed.

Inspection of the aorta and the ductus showed a friable area of aortic wall adjacent to the right wall of the ductus arteriosus. In dissecting the ductus away from the bronchus, the inflamed area had been torn and attempts to stem the flow of blood with clamps had only increased the size of the tear.

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Editorial

Skin Grafting and the Three-Quarter Thickness Skin Graft

ALTHOUGH skin grafting is one of the older surgical procedures, it is remarkable that the surgical profession generally has little knowledge of the good results which can be obtained in the alleviation of many soft tissue deformities by resurfacing the defect with a proper type of skin graft. The various specialty surgeons are more remiss in this respect than the general surgeon. Even many of the plastic surgeons (probably because of the publicity given the pedicled flap) are not always cognizant of the advantages of the usage of a properly selected skin graft.

A more or less simple surgical principle, preparation of a granulating surface for the reception of a skin graft, is often neglected. The fact is lost sight of that a granulating surface has to be surgically clean if a "take" of the skin graft is to be expected and that for cleansing purposes in such instances nothing is superior to a wet antiseptic dressing changed repeatedly or immersion in an antiseptic solution followed by a moist antiseptic dressing.

If one has ever completely excised a heavy scar and noted how much larger the resultant wound is than the central scar, it is easy to understand how a scar tends to contract like rubber and thereby limits movement unless prevented from doing so by underlying anatomical structures. Still much too often this simple principle is not appreciated and therefore the remedy is overlooked; namely, completely replacing the epithelium that has been lost and thereby alleviating the dysfunction. When dealing with healed soft tissue lesions, often there are two reasons for hesitation; either the operator is not dexterous enough to remove a proper graft or he fears the failure of a take.

A new epoch in skin grafting was heralded in 1929 when Blair and Brown introduced their more or less superficial intermediate skin graft, the so-called split graft. Their idea was that one might gain some of the advantages of the full thickness skin graft so far as the properties of good appearance, relative lack of contracture, and fair protection were concerned and that the factor of uncertainty of a perfect take might be eliminated largely as it is with the so-called Thiersch graft. In other words, by cutting a graft considerably thinner than the old full thickness graft and somewhat thicker than the type of skin grafts formerly used, the good properties of each might be combined in this new type of graft and most of the disadvantageous properties might be largely eliminated.

The ideal skin graft should be of such thinness as to assure successful transplantation and leave the donor site capable of spontaneous regeneration and yet be of such thickness as to afford adequate protection and minimum contraction and to match relatively satisfactorily the surrounding skin so far as texture and color are concerned.

However, anyone who has attempted to take an ideal piece of skin with a large knife will admit that often he does not succeed. Besides the inherent human factor and impossibility of controlling absolutely the level of a hand-held knife, much depends upon such factors as the location of the area from which the graft is being removed, the nutrition of the patient, the sex of the patient, the age and even the race. After measuring the thickness of cross sections of a large series of skin grafts taken from the adult male cut with the large skin knife and striking an average, one must conclude that as a rule grafts cut by the hand method, even when trying for depth, vary from 0.008 to 0.016 inch in thickness. Full thickness skin grafts cut by the scalpel in an adult vary from 0.032 to 0.040 inch in thickness.

From microscopic studies it appears that ideally in an adult at least one should be able to sever the skin at a level of from 0.020 to 0.024 inch to get sufficient thickness to approach the qualities of the full thickness graft and still retain the two outstanding good qualities of the superficial intermediate skin; namely, comparative certainty of "take" and the retention of sufficient epithelial elements in the donor bed for re-epithelization. The ideal graft, therefore, to apply on a clean raw surface is a three-quarter thickness skin graft cut at a level from 75 to 90 per cent of the thickness of the skin.

Recently a dermatome has been constructed which, with the utmost facility and ease, allows one to remove a sheet of skin as large as the drum of the dermatoma (4 by 8 inches) and to cut it absolutely of uniform thickness. The thickness can be varied and set at a predetermined level by a calibrating mechanism.

The main advantage of the three-quarter thickness skin graft cut with the dermatome (thickness of 0.020 to 0.024 inch) over the full thickness skin graft on clinical trial has proved to be that a take is a practical certainty if the other factors are observed, such as proper fixation, tension, hemostasis, pressure, and a clean field. Most of the inadequacy of take in the 20 per cent or more of attempts at full thickness skin grafting in difficult areas seems to have been eliminated.

The factor of increased certainty of take has allowed the surgeon to extend the indications for thick skin grafting. It has allowed him to graft successfully such areas as the dorsal and ventral surfaces of the hand and about and between the fingers. Especially in the correction of marked cicatricial deformity about the larger joints, such as the axilla, and also in the correction of other contractures and blemishes,

he can gain greater correction by the use of a three-quarter thickness skin graft of uniform thickness because of the certainty of a take. The fact that one encounters few blistered areas or areas of necrosis so that the subsequent texture and the color are as good as when one gets a partial take improves the functional and cosmetic results, especially on the face and neck. Finally, the fact that the donor area heals within ten to fourteen days from the base is of considerable advantage.

In several situations the thinner type of calibrated graft as removed by the dermatome (0.010 [0.25 mm.] to 0.014 inch [0.36 mm.] in thickness) has distinct advantages over the thinner types of grafts used in the past. Foremost, it allows one to graft successfully the individual with extremely wide denuded areas, a type of case which in the past has often presented a nearly hopeless problem to the surgeon because of his inability to obtain sufficient skin to cover the denuded areas; for example, the type of case with a tremendously large denuded surface covering both thighs and legs with most of the remaining skin on the trunk. The use of the dermatome allows one to remove skin from the abdomen, the chest, the back, or buttocks. It seems that one may use a slightly thicker type of graft (0.014 [0.36 mm.] to 0.016 inch [0.45 mm.] in thickness for example) on a granulating surface so that ultimately the amount of contracture is less and the cosmetic appearance is better. Thus, for the routine case in which it has been customary to use successfully the types of grafts as cut with the large knife, the ease, the accuracy, and the quickness of the method recommend the dermatome-cut graft as preferable. In grafting a large cavity it is particularly advantageous to have a large sheet of skin of uniform thickness to drape over the stent. On a small baby one cannot cut by hand with a skin graft knife a graft of sufficient size to be very useful if a large defect is to be covered. With the dermatome a graft of large size may be taken from either the abdomen or the chest. The same may be said in the case of a graft cut from an emaciated person, such as may occur when one sees a severe burn after several months.

Further, if one can vary the thickness of the graft at will, depending upon the region to which it is to be applied and the lesion which one aims to correct, it should prove desirable for varying lesions in different locations to cut a graft of a thickness or a thinness as indicated. And again, according to the age of the patient and the particular region from which the skin is to be removed, a variation in thickness should be desirable as it is well known that the skin of children is thinner than that of adults and that the skin in certain regions, such as the inner thigh of a woman, is thinner. As previously mentioned, for certain lesions it is evident that, if one could remove the skin from any area of the body, such as the chest, the back, or over the ribs, certain areas could be resurfaced in a way not possible by the use of methods commonly practiced.

Finally, and probably most important, due to the invention of the dermatome a new skin graft has become available, a three-quarter thickness skin graft, cut at a level of from 75 to 90 per cent of the thickness of the skin. This graft has advantages over the so-called full thickness skin graft and the superficial intermediate skin graft, especially for giving adequate coverage of aseptic denuded surfaces. The ease with which a skin graft of any thickness may be removed even from areas not previously available simplifies the whole art of skin grafting.

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Kansas City, Mo.

Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

RECENT ADVANCES IN THE STUDY AND MANAGEMENT OF TRAUMATIC SHOCK

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(From the John Simon Guggenheim Memorial Foundation and the Department of Surgery, Division of General Surgery, Henry Ford Hospital)

(Continued from the March issue.)

f. *Plasma (or Serum).*—The transfusion of plasma or serum is not new, being used experimentally by Bowditch (1871) and Luciani (1872). The value of plasma in restoring blood volume after hemorrhage was known to Rous and Turner as long ago as 1918. Plasma has been advised since then by many, including Heinatz and Sokolow (1935); Filatov and Kartaševskij (1935), of the Leningrad Blood Transfusion Institute; an annotation in the *Lancet* (1939); Knott and Koerner (1939); Elliott, Tatum, and Nesset (1940); Elman (1940); Fine and Gendel (1940), in experimental intestinal obstruction; De Gowin, Hardin, and Plass (1940); and others listed elsewhere in this paper. The importance of plasma loss in shock has already been discussed. Its importance in other conditions is also to be reckoned with. The effect of hypoproteinemia in wound disruption has been worked out by Thompson, Ravdin, Rhoads, and Frank (1938).

The observations of Brennan (1940) offer new evidence for the benefit of plasma transfusions. This writer found that: (1) As a result of hemorrhage the individual red blood corpuscles increase very appreciably in size, often by 30 to 50 per cent or more. (2) Following hemorrhage very considerable numbers of the patient's red blood corpuscles become sidetracked within the body, probably in the muscle capillaries. Often more than 20 per cent of the number of those originally circulating were found to be "missing" in this way. Brennan considers that this is because of the inflow into the blood stream of tissue juices of low osmotic pressure which later enter the corpuscles, causing them to swell and clog the capillaries. If these corpuscles could be restored to the circulation, they would correspond to the number that would have been given by the transfusion of a liter of whole blood. Brennan then shows in sixteen cases, mainly neurosurgical patients with extensive blood loss, that plasma transfusions will accomplish this return of lost red cells, and these are in reality a type of autotransfusion.

In these cases plasma from stored blood was diluted half-and-half with normal saline solution and given rapidly, 500 c.c. in 20 to 35 minutes. Serial red counts and mean corpuscular volume determinations indicated that, following the plasma administration the red cell count increased appreciably, while the mean corpuscular volume returned to normal. Thus, in one case a liter of plasma was given, and over a two-and-one-half-hour period, the red cell count increased gradually from 3.2 millions to 4.2 millions. In another case:

	R.B.C. IN MILLIONS	MEAN CORPUSCULAR VOLUME (μ^2)
Preoperative	5.5	85.4
Before plasma	3.4	134.8
After plasma	4.6	91.1

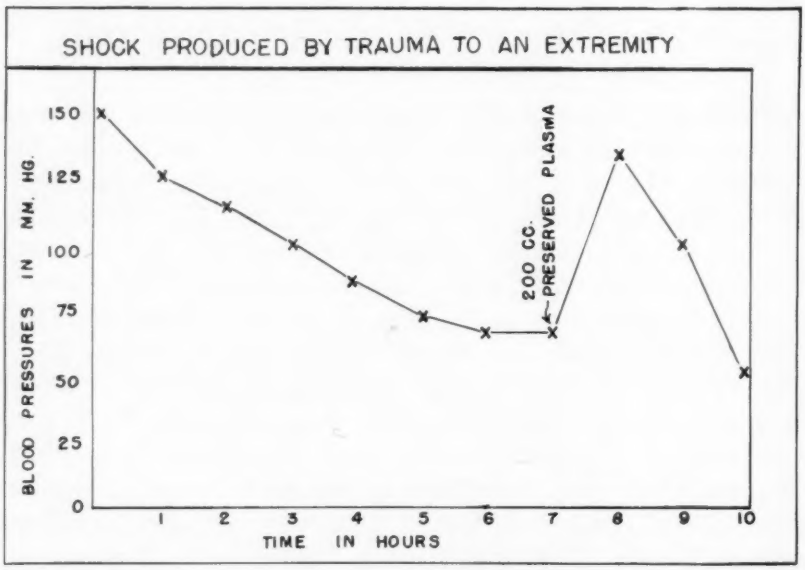

Fig. 7.—Temporary blood pressure response to injection of preserved plasma. Result in an experimental animal. (From Mahoney, E. B.: Ann. Surg. **108**: 190, 1938. Courtesy J. B. Lippincott Co.)

This work is of tremendous interest, but unfortunately no controls were presented. Not only was the possibility that such changes might have occurred spontaneously not discussed, but no mention is made of the possible role of the spleen.

The *separation of plasma from cells* has been accomplished in several ways. In 1936 Elliott, who already was aware of the advantages of plasma transfusion, used a vacuum bulb tube, sealed at both ends with rubber, which could be perforated with a needle for collecting blood. After the period of safety for whole blood storage had elapsed, the rubber at the bottom was perforated with a needle, the cells drawn off, and the plasma then preserved in the original tube for an indefinite period. Scudder, Bishop, and Drew (1940) used their hourglass container, drawing off the plasma after a week into a separate container.

While this method has the advantage of small interface, due to hourglass construction, the plasma runs the risk of contamination in being removed from one bottle to another. The method of Crowley (1940), as shown in Figs. 8, 9, 10, and 11, combines the advantages of both the above methods. A double bulb with a narrow neck or crossbar about two inches long and a projection upward from the top of one of the bulbs (thus dumbell-shaped with the crossbow extended beyond one of the bells), made of sodium glass of low melting point and containing the correct amount of citrate solution, is sterilized in an autoclave. Drawn blood is introduced directly through the open tube at the top of one of the bulbs to the bottom of the other bulb with a long filling needle below the citrate level. The two bulbs are filled, but the volume of the lower

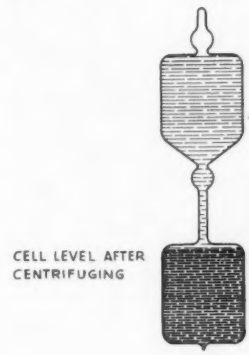

Fig. 8.

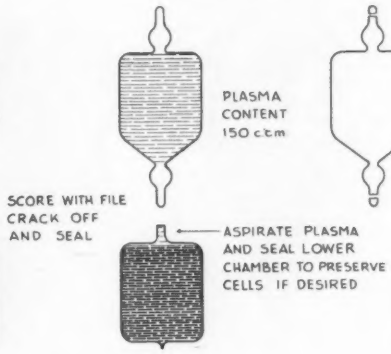
SCORE WITH FILE CRACK OFF AND SEAL
PLASMA CONTENT 150 c.c.m
ASPIRATE PLASMA AND SEAL LOWER CHAMBER TO PRESERVE CELLS IF DESIRED

Fig. 9.

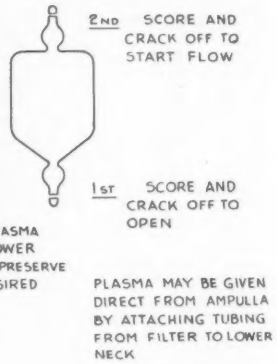
2ND SCORE AND CRACK OFF TO START FLOW
1ST SCORE AND CRACK OFF TO OPEN
PLASMA MAY BE GIVEN DIRECT FROM AMPULLA BY ATTACHING TUBING FROM FILTER TO LOWER NECK

Fig. 10.

Fig. 8.—Ampul tube method of preparing sterile citrated blood plasma. Centrifuged. (From Crowley, R. T.: Surg., Gynec. & Obst. **71**: 778, 1940. By courtesy of *Surgery, Gynecology and Obstetrics.*)

Fig. 9.—Ampul tube method of preparing sterile citrated blood plasma. Sealed ampule. (From Crowley, R. T.: Surg., Gynec. & Obst. **71**: 778, 1940. By courtesy of *Surgery, Gynecology and Obstetrics.*)

Fig. 10.—Ampul tube method of preparing sterile citrated blood plasma. Opening. (From Crowley, R. T.: Surg., Gynec. & Obst. **71**: 778, 1940. By courtesy of *Surgery, Gynecology and Obstetrics.*)

bulb is such that after centrifuging the cell plasma interface preferably will be in the connecting tube. The open top is flame sealed, the two bulbs centrifuged, the crossbar scored with a file and broken at the plasma side of the interface, the plasma-containing top bulb inverted, and the just-opened end of the crossbar sealed. For administration, either end of the glass-sealed plasma chamber is opened, is attached to an intravenous outfit, and the other end opened. A filter should be used. The plasma chamber can contain 250 c.c. This method combines the advantages of preservation in the original container with small cell plasma interface.

That transfer of plasma from one bottle to another does not necessarily result in contamination, however, is shown by the excellent results of Elliott and Nessett (1940) and Tatum, Elliott, and Nessett (1939). These writers stored blood taken directly into Baxter transfuso vac containers. Of 515 specimens of blood cultured after storage of from one

day to four months, only 1 showed contamination. Following this, 286 specimens of blood were drawn off into centrifuge tubes, and then after centrifuging the supernatant plasma, drawn off into another vacoliter flask. Not a single contaminated specimen resulted despite the double transfer. The use of 1:10,000 merthiolate may explain these excellent results. Elliott, Busby, and Tatum (1940) reported 482 plasma infusions with only 3 reactions. Sturgis (1940) found 1:10,000 merthiolate

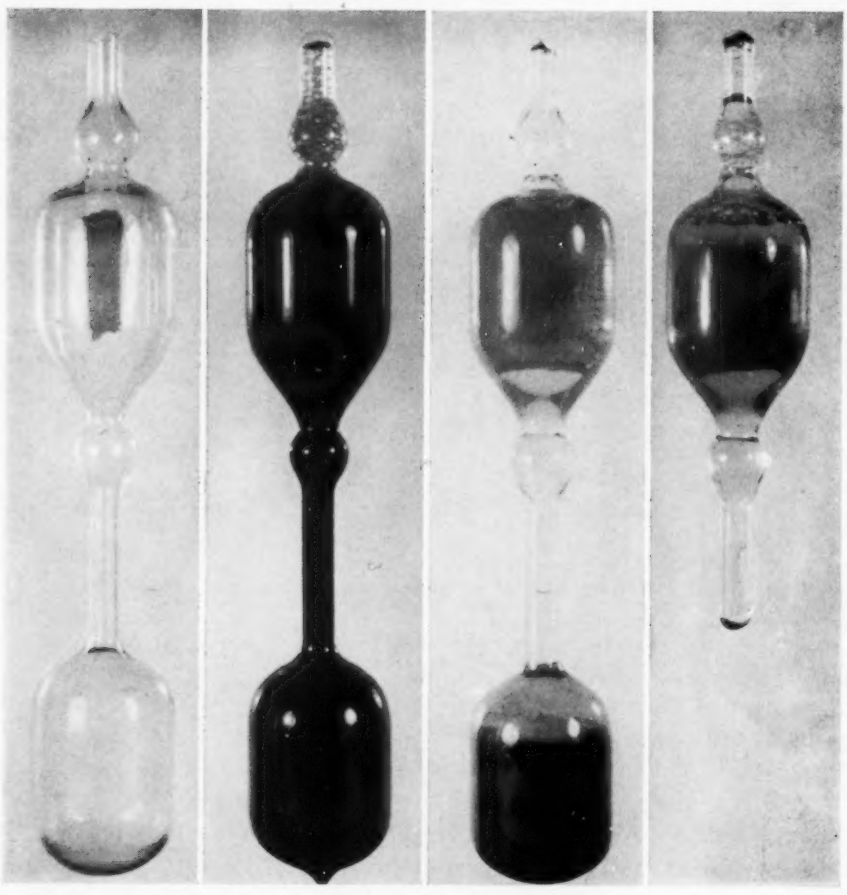

Fig. 11.—The same. Photographs of ampul tubes in process of preparation. (From Crowley, R. T.: Surg., Gynec. & Obst. 71: 779, 1940. By courtesy of *Surgery, Gynecology and Obstetrics.*)

to be of little value. One of the newest innovations in the field of serum and plasma therapy of shock is the recent placing of these substances on the market. Thus, one commercial firm offers either human plasma or human serum already prepared in "saftiflasks" in 250 c.c. amounts at $34.80 per flask.

Bushby, Buttle, and Whitby (1940) found that filtration of plasma through crude asbestos causes clotting due to some unknown factor that can be removed from the asbestos by treatment with 2 N nitric acid. Pure crystalline asbestos (Gooch fiber) does not cause clotting.

Neuwelt, Levinson, Olson, and Necheles (1940) found that successive hemorrhages in dogs and only partial restoration with serum or blood do not permit survival of all animals, while reinfusion with amounts of serum or blood equal to the total volume of blood lost preserved the life of the animal in each instance. Their experiments furthermore showed that serum and blood are of nearly equal value and that in shock from massive hemorrhage maximal rather than minimal amounts of serum or blood should be administered.

The new method of calculating the blood volume of a wounded patient by means of comparing the hematocrit before and after a plasma transfusion, as introduced by Bushby, Kekwick, and Whitby (1940), may have some practical value. A normal-sized man is found on the battlefield and the amount of blood lost is unknown. A plasma transfusion is given; he improves. The question is: Has the plasma transfusion been adequate? How much blood had he really lost? The formula is:

$$Vo = \frac{P \times H_2}{H_1 - H_2}, \text{ where}$$

Vo = Original blood volume just before plasma transfusion, the factor sought

P = volume of plasma given

H_1 = hematocrit just before plasma administration

H_2 = hematocrit just after plasma administration

EXAMPLE.—A man weighing 70 kg. and whose normal blood volume should be roughly 5,000 c.c. is brought in wounded. The hematocrit readings just before and just after transfusion of 1,000 c.c. of plasma are 44 and 32, respectively. Applying the above formula, the original blood volume on admission is

$$Vo = \frac{100 \times 32}{44 \times 32} = 2{,}666 \text{ c.c.}$$

which indicates that, even with the added 1,000 c.c., the blood volume is still 1,300+ below normal. This formula is open to the objection, however, that a difference of a few points in the hematocrit reading gives great differences in the blood volume. (Thus, with $H_2 = 34$, Vo = 3,400, $H_2 = 36$, Vo = 4,500, and $H_2 = 38$, Vo = 6,333!) This objection to the formula was not pointed out by Bushby and associates.

Serum Versus Plasma: This subject was discussed in a recent editorial (1940). Best and Solandt (1940) stated that as a result of their experimental work they were able to state that plasma and serum were therapeutically identical in shock treatment. Scudder (1940) favored the use of plasma over serum, believing it to be less toxic. Brodie (1900) observed experimentally that there was an immediate reaction to intravenous serum injection, the blood pressure falling. He found that in this regard "serum obtained from plasma is inactive." The use of plasma should be carefully differentiated from that of serum. That reactions occur after the use of lyophiled serum has been reported by Aldrich and co-workers (1938), Lehman (1939), and Ravdin and co-

workers (1940). These reactions have generally been attributed to serum changes induced by the lyophile process. Strumia, Wagner, and Monaghan (1940), however, pointed out that serum alone is much more likely to give reactions than plasma. Therefore, they believed that lyophiled plasma is the solution to this difficulty. It would seem that plasma may be preferable to serum. Prejudice against plasma probably arose in the days when citrate preservation was considered dangerous. Now we use it regularly for blood, why not for plasma? The effects of mechanically stirring or otherwise separating serum are much less physiologic.

Several writers prefer serum. Thus, Levinson, Neuwelt, and Necheles (1940) (experimental article) and Levinson, Rubovits, and Necheles (1940) (clinical article) favor serum, reporting a low reaction rate. It must be pointed out, however, that their evidence is based on smaller dosages than Strumia's plasma dosages. Clegg and Dible (1940) also favored the use of serum as opposed to plasma. They agree that in the stress of war both are preferable to whole blood, but that certain inherent disadvantages are present in the use of plasma. First, the fibrinogen fraction is unstable and tends to precipitate more and more on standing. In consequence the plasma solution comes to contain particulate matter, making the use of a straining filter essential for its administration. This keeps the plasma mixture from being safely given through a simple tube and funnel in an emergency where more complicated methods, which incorporate a filter in the system, are not available. Second, the separation of plasma from cells involves a good deal of manipulation with a considerable chance of contamination.

Clegg and Dible therefore decided to *convert their plasma into serum.* The serum would combine the advantages of: (1) being able to be given without typing; (2) containing no particulate matter even after long storage at either room or icebox temperature; (3) requiring no filter for administration; (4) being made from bank blood; and (5) passing through a bacterial filter, insuring its sterility.

Advantages 1 and 4 are inherent in plasma as well, and all but the fourth are present in the use of natural serum. Natural serum, however, cannot be made from bank blood. The usual methods of filtering plasma-saline mixtures have proved unsuitable for large-scale and wartime work. As reported by Bushby, Buttle, and Whitby (1940) and others, either the filter becomes clogged or the filtrate, at first clear, later develops a precipitate on standing. Clegg and Dible therefore developed the following technique:

Blood is taken from Group A and Group O donors into a standard bottle of 540 c.c. capacity containing 180 c.c. of 1.05 per cent sodium citrate in 0.85 per cent sodium chloride. The blood is stored in the ice chest for seven to ten days, during which period it is available for transfusion. If not used, the supernatant plasma-citrate-saline mixture is removed by suction in a closed circuit, pooled, and the fibrin pre-

cipitated by the addition of calcium chloride. Twenty cubic centimeters of 8 per cent sterile calcium chloride per liter of plasma are added with glass beads and the mixture placed in a mechanical shaker. A firm clot separates; the supernatant serum is filtered through a Seitz filter and stored in sterile containers. The resultant serum has the following composition:

Total protein	4.5 to 5.0 Gm./100 c.c.
Calcium	65.0 to 80.0 mg./100 c.c.
Potassium	38.0 to 40.0 mg./100 c.c.

The somewhat high potassium content of this mixture would be theoretically counteracted by the high sodium content. No ill effects have been attributed to the potassium in actual use. Quantities of this serum have been given up to 1,500 c.c. to shock and hemorrhage patients and normal subjects. The only reaction was a transitory urticaria and chill in a normal man given 1,000 c.c. intravenously in fifteen minutes.

Elman (1941) reviewed the use of plasma in severe burn shock. Brennan (1941) pointed out that the plasma requirements of shocked patients cannot always be calculated from a simple blood concentration index such as that of Bushby and associates (1940). Mobilization of sidetracked red cells may cause an actual concentration to follow plasma administration. Tidy (1940), discussing Black's (1940) index of the amount of plasma transfusion in burns on the basis of hematocrit readings, pointed out that the initial hematocrit is an assumption in this index. Hence it is only accurate if the patient's hemoglobin before the burn is normal. The extensive clinical experience with concentrated plasma reported by Hill, Muirhead, Ashworth, and Tigertt (1941) helps to place this mode of shock therapy on a sounder footing. These authors reported a reaction note of 1 per cent among 299 administrations of concentrated plasma. In 45 cases of shock the results were excellent.

Brown and Mollison (1940), in discussing the current argument regarding the relative merits of plasma and serum, point out that in their experience the dried serum emanating from the Medical Research Council's serum drying unit at Cambridge is not only safe but efficacious. The serum is passed through a Seitz filter before being dried from the frozen state *in vacuo*. In most cases four times normal serum was used. Because it took some time to reconstitute the serum, this process was often done the night before use. In my experience with dried plasma this would be dangerous as the reconstituted plasma tends to gel. Brown and Mollison gave their concentrated serum at room temperature, in doses of 40 to 500 c.c., with 34 reactions following 202 transfusions. In a series of 30 plasma transfusions 8 reactions occurred.

When plasma is given, it may be administered in several forms:

Natural Plasma: This was used by Lehman (1939) and others. Strumia, Wagner, and Monaghan (1940) used plasma in over 1,500 administrations without a reaction. In the present vogue for plasma transfusion it is interesting to note, as Robertson (1940) pointed out,

that excellent results were obtained during World War I by the use of cells resuspended in normal saline solution. It is doubtful, however, if these results can be compared with those of more recent times. Weech, Goettsch, and Reeves (1933) used serum transfusions experimentally in dogs for nonshock (nutritional edema, etc.) conditions. Recently Strumia (1940) stated that he believes that plasma transfusions are as useful as whole blood transfusions in all but one emergency clinical condition; that is, carbon monoxide poisoning. Strumia does not type his plasma and has had no reaction in over 1,500 administrations. He restricts its rate of administration to less than 10 c.c. per minute, although he has given 900 c.c. in thirty minutes without reaction.

Preserved Plasma: This is merely natural plasma obtained from a blood bank after the blood has been stored. Once separated from the cells, the plasma can be kept almost indefinitely, but it must be filtered before administration.

Recalcified Plasma: This is serum made from plasma according to the method of Clegg and Dible. Calcificated plasma might be a more accurate term.

Dried Plasma, Concentrated Plasma, Reconstituted Plasma: Dried plasma is a powder. Concentrated plasma is either partially dried plasma or dried plasma reconstituted up to less than its original volume. Reconstituted plasma is dried plasma redissolved in water. Edwards, Kay and Davie (1940), using a method of vacuum distillation without freezing, have recently introduced the use of dried plasma into the British Army. This report indicates the trend toward abandoning whole blood transfusion and substituting the more foolproof and almost, or even just, as effective plasma transfusion. Mudd, Flosdorf, Eagle, Stokes, and McGuinness reported the lyophile process in 1936. Preserved plasma was used experimentally by Mahoney (1938). He performed experiments on the treatment of shock due to peritoneal cooling and to trauma to an extremity. Referring to the former, he stated: "Preserved plasma was compared with whole blood, saline and acacia in the treatment of this type of shock. The plasma was found to be the most efficient therapeutic agent in restoring the normal blood pressure." He found the plasma less efficient in treating shock due to trauma to an extremity.

That serum preserved by the lyophile process can be safely used in large amounts in human beings is attested by the beneficial effects of its administration in a series of lipoid nephrosis patients treated by Aldrich, Stokes, Killingsworth, and McGuinness (1938). In these patients a marked diuresis followed the injection of four times concentrated serum. In a second paper Aldrich and Boyle (1940) confirmed these results. Freeman and Wallace (1838) studied experimentally the effect of concentrated serum on the plasma volume and serum protein concentration. Thalhimer (1939) described a method for concentrating serum in cellophane bags and in a later paper described

a method for drying the serum in the frozen state in cellophane bags. The report of Bond and Wright (1938) on the use of lyophile serum in the treatment of experimental shock and hemorrhage is one of the most convincing bits of evidence in favor of this mode of treatment. Flosdorf and Mudd (1938) have introduced a new type of serum to take the place of the lyophile process; namely, the cryochem serum (from κρύος + χημια) to designate evacuation *in vacuo* from the frozen state. This new process depends on $CaSO_4$ freezing instead of solid carbon dioxide, and reduces the price of a liter of serum from $3.00 to $20.00 (by the lyophile process) to 75 cents (by the cryochem process). Amberg and Osterberg (1940) described another method of drying serum; namely, dialyzation against an acacia solution. They must have found it unsatisfactory, because only seven months later Harper, Essex, and Osterberg (1940) reported on another method of preparation of dried plasma used in the Mayo Clinic. This consisted in simple distillation of the plasma at 45° C. with additional bubbling of sterile air through the plasma. About 400 c.c. could be dried in an hour, and experiments on the final product (using dried dog plasma redissolved) on dogs revealed that it was without reaction when uncontaminated with serum. Dried human plasma, when redissolved, likewise gave no untoward reaction. This method is much simpler and cheaper than the lyophile method.

Methods of Preparing Dried Plasma (or Serum): Besides the lyophile and cryochem processes, the methods of Edwards, Kay, and Davie and of Thalhimer, and the two processes used at the Mayo Clinic, numerous methods for manufacture of dried plasma or serum are in use. Preparation of dried serum was begun just at the close of the last war by Burrows and Cohn (1918), who dripped the serum into an evacuated bottle at about the rate that evaporation proceeded. Much the same principle had been used by Martin (1896), of Sydney, Australia, who used a Pasteur-Chamberland filter to drip the serum into the evacuated bottle. He found that under these circumstances the "serum can be desiccated as quickly as it will filter." A method similar to Martin's, only using a funnel with its tip drawn to a fine point, was used by Hartley, Eagleton, and Okell (1923), of the Wellcome Laboratories, London. Shackell (1909) was the first to use the principle of evacuation from the frozen state (sublimation). Greaves and Adair (1936) described a method of desiccation of serum *in vacuo,* the water vapor being removed by P_2O_5. Freezing occurs from evaporation alone, no refrigerants being used. The use of phosphorus pentoxide is not suitable for large volumes of serum, so in 1939 these authors devised a method of high vacuum evaporation in which an electrically measured amount of heat was fed to the frozen serum. This same article gives several other references to this same subject.

The adtevac process of Hill and Pfeiffer (1940), of Dallas, consists in evacuation of serum from the frozen state with additional adsorption of the water vapor with silica gel to hasten the process. Hill (1940) re-

TABLE XIII

METHODS OF PREPARING DRIED PLASMA OR SERUM: A CLASSIFICATION

I. *Spray distillation in vacuo (method of evaporation)*
   1. Martin, 1896
   2. Burrows and Cohn, 1918
   3. Hartley, Eagleton and Okell, 1923
   4. Edwards, Kay and Davie, 1940
   5. Aylward, Mainwaring and Wilkinson, 1940
   6. Harper, Essex, and Osterberg, 1940

II. *Evacuation from the frozen state (method of sublimation)*
   1. Shackell, 1909 (prefreezing; chemical desiccant: H_2SO_4)
   2. Greaves and Adair, 1936 (chemical desiccant: P_2O_5)
   3. Mudd, Flosdorf, Eagle, Stokes and McGuinness, 1936 (prefreezing; cold condensor desiccant: solid CO_2), expensive; suitable only for small quantities; *"lyophile process"*
   4. Flosdorf and Mudd, 1938 (self-freezing; chemical desiccant: $CaSO_4$), *"cryochem process"*
   5. Greaves and Adair, 1939 (no desiccant; electrically controlled application of heat)
   6. Hill and Pfeiffer, 1940 (self-freezing; physical adsorption desiccant: silica gel), *"adtevac process"*
   7. Flosdorf, Stokes, and Mudd, 1940 (mechanical desiccation; expensive apparatus; prefreezing optional), useful for large quantities

III. *Permeation of water through cellophane membrane (method of pervaporation)*
   1. Kober, 1917 (bag)
   2. Terry, 1939 (long tube)
   3. Thalhimer, 1939 (long tube), for concentration, warm air; for drying, frozen
   4. Aylward, Mainwaring and Wilkinson, 1940 (long tube)
   5. Best and Solandt, 1940 (long tube)
   6. Hartman and Hartman, 1940 (double surfaced cylinder with rotation), the "rotor pervaporator"

IV. *Miscellaneous methods*
   1. Amberg and Osterberg, 1940 (dialysis against acacia)
   2. Hall, Fader and Decherd, 1940 (alcohol-ether precipitation of proteins)

ported that he had given 115 doses of four-times concentrated plasma (9,900 c.c.) prepared by this method with only three transient reactions. Another method of preparing dried serum is that of Hall, Fader, and Decherd (1940), who precipitated the serum proteins with alcohol-ether solution. The serum proteins prepared by this method were injected into dogs and into a single human subject without serious reactions.

Before going on to a general discussion of more methods of drying plasma (or serum), a classification would be in order, as given in Table XIII. It is seen that the methods of evaporation and sublimation are merely modifications of the crudest of all methods, drying in an open dish. Sublimation works well, but excess water vapor is difficult to remove, as testified by the various means to overcome this difficulty. Of the methods of sublimation, the desivac process is best suited for large volume work, the drying capacity of a single unit being 100 liters of plasma a day. Such an apparatus would cost $18,000.00, while a 10 liter a day apparatus would cost $3,200.00. Of the methods of evaporation, if the unfrozen plasma is caused to bubble, the result seems better (e.g.,

present Mayo Clinic method). A summary of the methods of evaporation and sublimation is given by Mason (1940).

The first five methods of pervaporation listed in the table are all variants of Kober's original bag-before-a-fan method. Kober (1917) noted that "collodion and parchment membrane containers permit water to evaporate through the walls as though no membrane were present," and called this phenomenon "pervaporation." It could be hastened by fanning or by heat. This method works fine for *concentrating* plasma, but the last stages of *drying* are interminably long. Terry (1939), for example, merely concentrated and did not even try to dry. Hartman and Hartman (1940) combined the principle of *pervaporation* with that

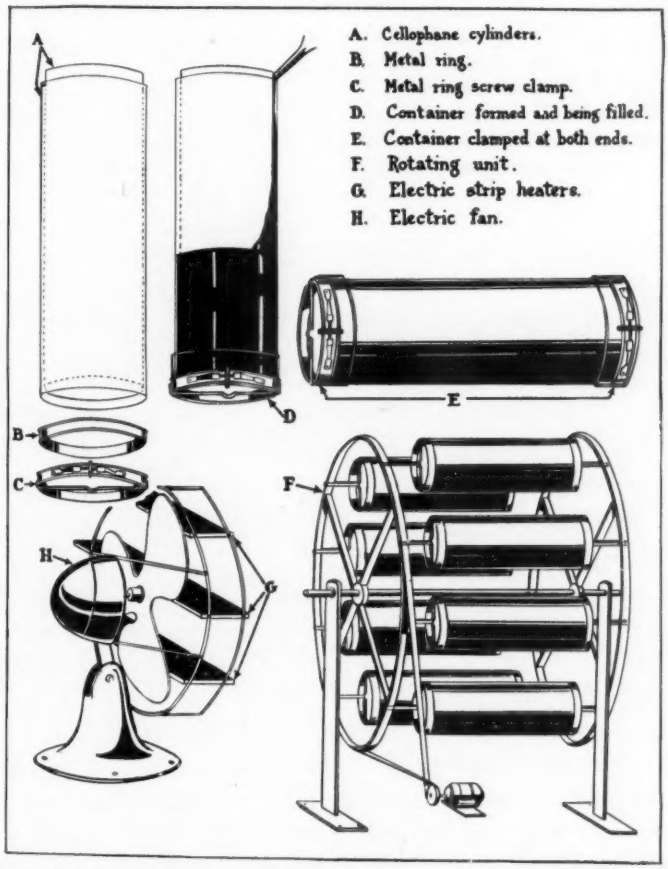

Fig. 12.—The Hartman rotor pervaporator apparatus for desiccating blood plasma. (From Hartman, F. W., and Hartman, F. W., Jr.: J. A. M. A. 115: 1990, 1940.)

of *stirring* in their "rotor plasma pervaporator," shown in Fig. 12. Constant rotation causes frothing with application of a constantly new fluid surface to the exposed cellophane walls. The frothing enables the plasma to be gently rubbed into an easily redissolved powder between the cellophane surfaces when dry; whereas, unfrozen plasma made in cellophane bags or tubes without rotation is apt to cake, and is difficult to put into solution again. This apparatus combines simplicity, econ-

omy, sterility, and rapidity. The double walling of the cylinders alone increases the drying area 100 per cent. While the cylinders usually are opened when needed, the powder poured out and reconstituted in the usual manner, in an emergency the cylinders can be immersed in tap water and the drying process reversed. With the smallest unit of this apparatus 5,400 c.c. of plasma may be evaporated at one time.

Use of Concentrated Plasma: Best and Solandt (1940) have extended the use of concentrated serum as used by Aldrich and associates for medical conditions (nephrosis, etc.) to the treatment of traumatic and histamine shock in experimental animals. They believed that the presence of abnormal amounts of fluid in certain tissues during shock is detrimental apart from the loss of blood volume which is represented. Treatment aimed at returning this fluid to the blood stream has long been attempted with hypertonic aqueous solutions. These solutions, however, are themselves apt to leak out through the vessel walls and reverse their action and do more harm than good. From the theoretical standpoint it would seem that concentrated serum might have the desired osmotic action without the deleterious side effects.

Best and Solandt tested this hypothesis on dogs with shock due to (1) histamine, (2) trauma plus hemorrhage, and (3) trauma, using serum concentrated to three times normal. They found that 20 per cent glucose, 3 per cent salt solution, or three times concentrated serum were all more effective in restoring blood pressure than their respective isotonic equivalents, but that the effect of the first two was much more transient than that of the concentrated serum. Finally, they found that a single intravenous dose of pituitrin just before the administration of an adequate quantity of concentrated blood serum seemed to be the best of the treatments studied.

On the other hand, Magladery, Solandt, and Best (1940) found that in posthemorrhagic shock isotonic serum was just as efficacious as concentrated serum. They found that in the treatment of posthemorrhagic shock in dogs approximately 40 per cent of the blood removed must be restored to secure recovery. Comparable volumes of serum or plasma produced equally satisfactory results. They concluded that in their experiments the volume of the red cells restored to the animal is more important than their oxygen-carrying capacity and that serum and plasma were as effective as whole blood. They advised a rapid rate of administration (50 to 100 c.c. per minute) as soon as possible after the hemorrhage of the serum or plasma.

Concentrated lyophile serum has been used by Hughes, Mudd, and Strecker (1938) and by Wright, Bond, and Hughes (1938) to reduce increased intracranial pressure.

With the British Army adopting plasma transfusions and with the idea in mind that Strumia has used over 1,500 of them without typing, it would seem that plasma transfusions should become the chief item in all shock treatment. Strumia, Wagner, and Monaghan (1940)

favored plasma transfusions even for hemorrhage, stating: "In cases of severe hemorrhages the loss of erythrocytes is a relatively secondary factor, one which contributes but little to the state of shock, provided the volume of circulating blood is maintained at a proper level." In their hospital blood is mixed with a 2 per cent solution of sodium citrate in normal saline solution in the proportion of 100 c.c. of citrate-saline mixture to 500 c.c. of blood. Plasma is separated by suction after centrifugation and may be used or stored at 4° C. after addition of merthiolate solution 1:10,000. The plasma is pooled and tested serologically by means of the Wassermann and Kahn tests, but it is not typed or cross-matched. Further discussion of plasma is given under the heading "Shock in Wartime."

3. Oxygen.—The importance of anoxia was stressed under that heading. At present, administration of oxygen gas from tanks, or better from the liquid state, into a tent or mask is the best method of administration. All shock patients should receive oxygen, possibly with 5 per cent carbon dioxide in cases where respiration is deficient.

4. Adrenal Cortical Extract.—The use of this substance either in the natural or synthetic form has already been discussed. While this method of treatment is still in the experimental stage, it seems to offer great promise. It may act either by reducing hyperpotassemia or by decreasing abnormal capillary permeability.

VII. SHOCK IN WARTIME

The tremendously renewed interest in this subject, not only in Europe, but in the United States, is at once apparent from a review of the literature during the past few months. The Medical Research Council (England) *The Treatment of Wound Shock, M. R. C. War Memorandum No. 1,* and the National Research Council (United States) *Bulletin on Shock* are especially important recent contributions. Recent emphasis seems to be on adopting treatment to modern mobile warfare, especially in the use of easily transportable preserved blood or blood factors.

The possibility of use of bovine plasma intravenously in man is discussed by Cohn (1940) and by Wangensteen, Hall, Kremen, and Stevens (1940).

A series of four articles from the Edinburgh and South-East Scotland Emergency Blood Transfusion Service deserves attention. New equipment was described by Stewart (1940) with a reaction rate of 13.6 per cent. Scarborough and Thompson (1940) studied the oxygen capacity of stored blood, concluding: "Neither the haemoglobin content nor the oxygen-capacity of blood is impaired to an important extent by storage under the conditions described for periods up to thirty days." In the final paper Crosbie and Scarborough (1940) found that ten days' storage caused 74 per cent of the leucocytes in blood to be destroyed.

The recent report of Maycock (1940) on the results of the nine blood transfusion services in the Battles of Flanders and France is of interest.

Few details are available about the use of plasma, of which there was comparatively little in Flanders. All the officers of the service stressed the advantage of giving adequate amounts and that failure of a severely wounded and shocked patient to recover after 2 to 3 pints of blood or plasma probably means that further quantities must be administered. The highly mobile type of warfare imposed great difficulties upon organization. The need for having each bottle of fluid accompanied by an apparatus for administration was essential under active service conditions.

The number of transfusions given can only be approximated, but it can be said that some 350 to 500 pints of stored blood and plasma were used between May 10 and the evacuation of Dunkerque. Certain technical points merit notice. Cannulation was seldom required (13 per cent at one casualty clearing station and 2 per cent at another), although large quantities of blood were given to single patients. Cannulae were of use during aerial bombardment when restlessness and nervousness increased among the wounded. Prolonged storing of blood, even seven weeks in one instance, seemed to make little difference and reactions were few. Likewise, transportation over rough roads, e.g., 100 miles from Arras to Brussels, seemed to exert no ill effect. The following quotation from one of the Service Chiefs is of interest: "Transfusions were given to patients in beds, on stretchers, in clean rooms, in hovels.... Asepsis did not exist, antisepsis in most cases was almost impossible to achieve. I am convinced as a result of this experience that a transfusion could be given in absolutely any circumstances except in a vehicle." And Maycock doubts the importance of this last restriction. Maycock finally concludes that either the wounded must be brought to the transfusion centers more quickly or the transfusions must be given nearer the battle line. Since blood requires refrigeration, this second objective is difficult to obtain without resorting to plasma. Brown, Dennison, Ross, and Divine (1940) also reported on the use of blood transfusions in the treatment of soldiers wounded in the battle of Flanders.

The method of blood transfusion described by Bashford (1940) is very applicable to rural or wartime conditions where hospital facilities are not obtainable. Yott (1940) described a method of collecting blood by suction and of administration by pressure which requires only one bottle and hence reduces the chances of contamination and would possibly have a wartime application.

Brewer, Maizels, Oliver, and Vaughan (1940) have recently presented a study on the relative merits of fresh and stored blood. This work comes from the four London Blood Supply Depots (N.E., S.E., S.W., and N.W.). All blood used was obtained from the four depots. Two parts of blood were added to one part of diluent, consisting of 3 per cent glucose in 0.85 per cent sodium chloride and 1.05 per cent sodium citrate. They defined fresh blood as that stored for less than twenty-four hours and stored blood as that more than twenty-four hours old. For acute conditions they found stored blood as useful as fresh blood. For some

of the more chronic cases fresh blood may have been a little better, but not much. Mild reactions occurred more commonly following the use of stored blood than after fresh blood, but severe rigors were practically identical in the two cases (4.7 and 5.4 per cent, respectively). These authors concluded that stored blood should be heated to 37° C. before use, but this conclusion is based on a comparison of only 56 warmed blood specimens with 39 unheated specimens. Furthermore, all reaction rates were higher than in certain other series.

De Gowin, Hardin, and Plass (1940), discussing the storage and transportation of blood for military purposes, stated that blood shipped by transport plane from Iowa City to Oakland, Calif., and return (3,539 miles) was essentially unhemolyzed and reaction-free. Similarly, blood sent by hospital ambulances 500 miles was unharmed. It was found practical to pack ten flasks of blood and the necessary ice in ten-gallon milk cans surrounded by commercial insulating covers. This obviates the use of special equipment in an emergency.

Scudder (1940) and Sturgis (1940) recently summarized the use of plasma in the United States. The latter stated: "I believe ultimately we will be using desiccated plasma in the treatment of shock, probably not diluted up to normal strength, as this will increase the osmotic pressure in the vascular system." Sturgis states that centrifuging of blood to obtain plasma is apt to generate heat causing hemolysis. This can be overcome by the use of dry ice or by using simple settling, the latter giving an approximately 75 per cent plasma yield. Scudder has found the pH of plasma obtained by settling to be nearer normal than that obtained by centrifuging.

Certain very recent publications on the nature of shock may eventually have a wartime application. The observation of Salmon and Engel (1940) that pantothenic acid prevents certain types of hemorrhagic adrenal necrosis due to deficiency states may lead to further discoveries. The recent review of shock by Grodins and Freeman (1941) is of interest. The use of the intramedullary route (into the bone marrow of the sternum, clavicle, tibia, or femur) by Tocantins and O'Neill (1940) is of great interest. These authors used this method in 13 patients. Citrated blood, plasma, glucose and salt solutions were infused without any immediate or delayed local or constitutional reactions.

Rose and Browne (1941) found from experiments on the rat that there is a marked increase in the histamine content of the gastrointestinal tract and a lesser increase in the histamine content of the liver and lung following adrenalectomy. These results may indicate that histamine may bear a relationship to the production of symptoms of adrenal insufficiency and shock and that the metabolism of histamine is influenced by the cortex of the adrenal gland. Boyd, Stevenson, and Watkinson (1938) showed that removal of one-quarter of blood volume of rabbits by hemorrhage did not produce a leucocytosis. Parkins, Swingle, Taylor, and Hays (1938) found that administration of adrenal

cortical hormone was beneficial in adrenalin shock in adrenalectomized dogs. Best and McHenry (1940) have cast a disparaging note on the wave of enthusiasm over histaminase stating that their observations led them to believe that "there was no physiologic basis on which to rest its clinical use."

Williams (1940), working at the Merseyside War Blood Bank, pointed out that, if blood bank bottles were autoclaved along with included citrate solution, the action of the citrate solution on the glass gave rise to an increased alkalinity. This alkalinity leads to hemolysis, but, if the bottles are autoclaved dry, sterility is difficult to obtain, especially as regards the absence of the organism *B. subtilis*. To get around the difficulty, a small amount of distilled water was included in the bottles at the time of sterilization.

The paper of Hill, McMichael, and Sharpey-Schafer (1940) is of great practical as well as fundamental importance. These authors made observations of hemoglobin concentration, blood volume, and blood pressure before and after infusion with normal saline solution, hypertonic saline solution, serum, or concentrated serum in patients with postoperative and post-traumatic shock. They found that physiologic or hypertonic saline solution given intravenously to normal people is rapidly lost from the circulation, while serum is retained in the circulation for long periods. The rise in blood volume is dependent on the quantity of protein added and is not increased by further dilution of the serum. These authors further found that in shocked patients intravenous saline produces transient benefit only, while serum is quite effective. They found the continued elevation of pulse rate in a shocked patient after restoration of blood volume and blood pressure not to be of dangerous import. They believed a rising hemoglobin in shock to be a bad sign while a falling hemoglobin in the absence of hemorrhage is a good sign. Finally, they believed that the retention of infused serum or saline solution can be gauged by observing the changes in the hemoglobin percentage.

The recent article of Solandt (1941) on the work of a London Emergency Blood Supply Depot (of which he directed the S. W. section) is of interest. The S. W. Depot is one of the four London depots and bleeds about 600 to 700 donors a week. Some whole blood is used for transfusion, some plasma is filtered at the Wellcome Laboratories, and the rest of the blood is used for preparation of serum for drying at Cambridge. A blood "depot" and a blood "bank" are essentially the same. The depot system obviates the necessity of bleeding at night or on Sundays and this system has a great advantage when night transport for donors is made very difficult and even dangerous by the blackout and the barrage. Solandt states that it seems likely that "serum will largely replace plasma" in shock treatment. Stetten (1941) discussed the activities of New York City hospitals in sending plasma to Great Britain.

The British M. R. C. Memorandum summarizes its opinion of shock treatment by stating: "It is now generally accepted that the most important requirement for arresting the progressive deterioration in general condition which is such a feature of shock, is restoration of blood-volume and thereby of tissue metabolism." While I might tend to be prejudiced in favor of this statement, I must point out that the question of shock is not yet settled, and, while transfusion therapy is helpful, it is not the entire solution of the problem.

VIII. COMMENT AND CONCLUSIONS

A brief definition of shock is the following: A progressive vasoconstrictive oligemic anoxia.

A more descriptive definition of shock is: An oligemia *initiated by* traumatic local fluid loss, either whole blood, plasma, or both; *accompanied by* decreased cardiac output, diminished volume flow, lowered venous pressure, decreased oxygen consumption, arteriolar vasoconstriction, progressive hemoconcentration, capillary congestion, acapnia, and secondary blood pressure fall; and *perpetuated by* a summation of these factors and possibly hyperpotassemia, increased generalized capillary permeability, anoxia, action of tissue metabolites, and deficiency of adrenal cortical hormone. Other changes, both chemical and pathologic, often occur in shock, including increased blood nonprotein nitrogen, decreased coagulability of the blood, and in some instances increase in plasma magnesium.

With all of these changes going on, it is often difficult to tell which are initiating, accompanying, or perpetuating factors. In different clinical conditions the proportionate importance of different causative factors may vary and in some more than one cause may be active. The simplest case seems to be hemorrhagic shock where the loss of fluid is the initiating factor and the other changes act in an accompanying or a perpetuating role. In other cases the loss is chiefly plasma (e.g., burn shock), and in still others it is both whole blood and plasma (e.g., traumatic shock). In some instances the loss of fluid is gradual; in others it is sudden; in some it is greater than in others. In these latter some additional causative factor would seem to be active in producing death; whereas, when the fluid loss is large, it alone may explain the onset of shock and resultant death.

The primary result of the fluid loss is an oligemia with associated vasoconstriction, decreased cardiac output, and decreased blood flow. This latter factor is important in producing an anoxia and resultant general capillary wall and cell injury. A progressive hemoconcentration usually results from the general capillary wall injury and the attendant hyperpotassemia may result from general cell injury. The relations between these and other possible perpetuating factors have been discussed.

In the treatment of shock two aims stand out: (1) Replace what fluid has been lost and (2) prevent further fluid loss. The first aim can be best attained by adequate blood or plasma transfusion. The advantages in plasma transfusions in safety, simplicity, preservability, and portability may outweigh the more economical whole blood transfusions. Normal salt solution may be given along with the blood or plasma in moderate amounts but not as a substitute for them. The prevention of further fluid loss is the most difficult aim of treatment to fulfill. The well-known irreversibility of advanced shock is best evidenced by the case of even simple hemorrhage where after shock has existed for a time the replacement of even more blood than was lost is of no avail. The two chief remedies that are at present available in this regard are oxygen and adrenal cortical extract. Both are still in the experimental stage but offer considerable promise. Oxygen may act in preventing anoxia, while adrenal cortical extract may prevent increased permeability of capillary wall and cell membranes and prevent a possible hyperpotassemia. In all cases the chief aim of shock treatment should be to diagnose and to treat the condition in its early stages before such irreversibility has taken place.

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Book Reviews

Cirugia de la Constipacion. By Dr. Conrado Zuckermann, of the Mexican Academy of Surgery, Professor of Surgical Pathology of the Medical Faculty of Mexico and Surgeon of the Mexican Clinic of Surgery and Radiotherapy. Pp. 189, with 32 illustrations. Mexico, D. F., 1939, Manuel Leon Sanchez.

This monograph represents the work for which the author was awarded the Ricardo Arias medal at the Third Central American Medical Congress in October, 1935. First are presented certain factors thought to be of importance in the etiology of constipation. These include hereditary factors, errors of conduction, errors in alimentation, and local factors, such as parasites and neoplasms. The author stresses the frequency with which constipation is caused by Jackson's veil and various pericolic bands and adhesions. Therapy in milder cases is based on correction of hygienic and dietary faults together with physiotherapy and medications. Cases which fail to respond to these measures fall into the surgical group if accompanied by severe gas pains, toxemia, ptosis, or bands and adhesions. The simplest surgical procedure consists of appendectomy with cololysis or colopexy; a second group requires a short-circuiting procedure; and in a third group hemicolectomy or complete extirpation of the colon is chosen by the author, who favors spinal anesthesia, wide anastomoses of the open type, and the use of No. 0 or 1 chromic catgut for intestinal suture material.

There follows a chapter dealing with physiology of the large bowel and then a discussion of the various types of sympathectomy for relief of constipation with a description of surgical technique. The next chapter consists of abstracts of pertinent literature beginning with 1923 through 1936. Twenty case histories then are presented with discussion of the surgical procedures employed and the results obtained. In the summary the author claims excellent results in twelve of these cases, satisfactory results in four, and moderate relief in the other four. Many surgeons in this country will criticize the author for his use of heavy chromic catgut in intestinal anastomosis, while others will remain unconvinced that chronic constipation is a surgical disease. The monograph is well written and interesting.

Treatment in General Practice. Surgery Articles published from the *British Medical Journal*, Volume IV, page 562, with 143 illustrations. London, 1940, H. K. Lewis and Co., Ltd. 16s.

This volume consists of a number of articles published in the British Medical Journal between July, 1938, and May, 1940. While almost every field of surgery is discussed, articles concerning fractures seem to predominate.

As one would expect in a book of this type, there is no uniformity of style or method of approach to the subject matter, which gives the book a sense of being disjointed; nevertheless, the articles are well written. The tone of the volume is authoritative. The subject matter is of general interest and will appeal most to the general practitioner. The illustrations are fair. A workable index is appended.